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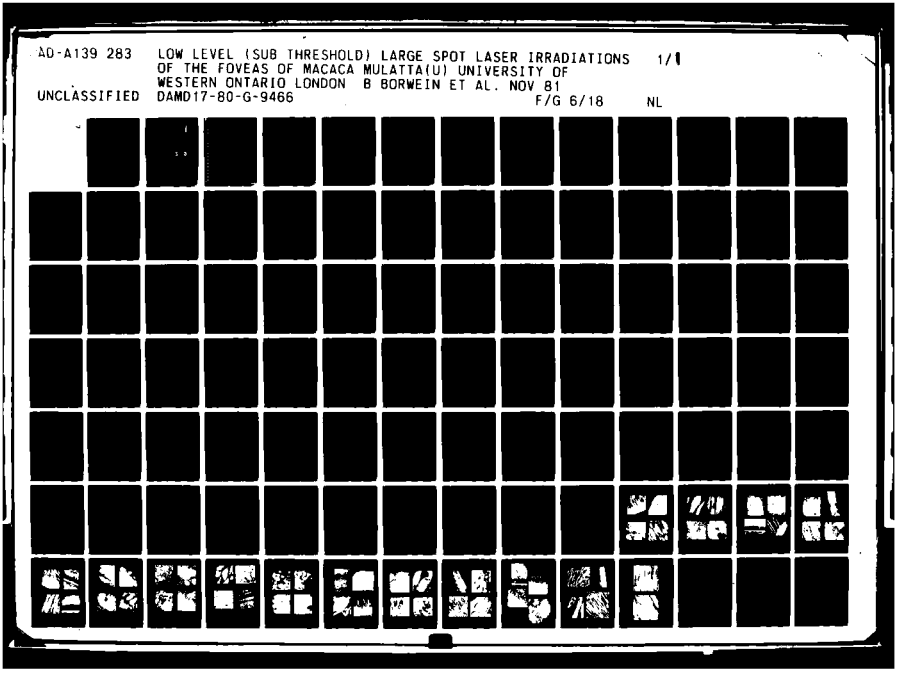

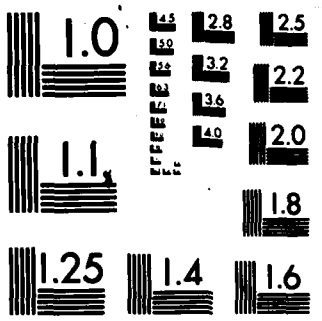

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Low Level (Sub Threshold), Large Spot Laser Irradiations of the Foveas of Macaca Mulatta

Final Comprehensive Report

Bessie Borwein
Martin J. Hollenberg

November 1981

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

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Eyes of 2 Macaca mulatta monkeys were used. 2 eyes were exposed to focal gallium arsenide and neodymium laser irradiations and 1 eye to whole eye cumulative argon irradiations. One eye was patched to act as a control.

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INTRODUCTION

The aim of this project was to study the effects of low level (subthreshold) large spot gallium arsenide and neodymium laser irradiations on the posterior retinas (including the fovea) of one rhesus monkey and the effects on the retina of whole-eye cumulatives exposures to argon irradiation on another monkey. One eye was patched to act as a control, and normal non-irradiated portions of the focally irradiated eye also acted as control tissue. In addition, the eyes of a Macaca fascicularis monkey became available to us (without charge) at the University of Western Ontario from a research project in another department and that also acted as control tissue.

We have completed a base line study of the normal receptors of Macaca monkeys (Borwein et al., 1980) against which the alterations induced by the laser irradiations could be compared.

The results are being submitted to ARVO, and to Investigative Ophthalmology and Visual Science.

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RESEARCH REPORT

METHODS

4 Rhesus monkey eyes from two animals were treated in the following manner at the Letterman Army Institute of Research, San Francisco, and one Macaca fascicularis at our laboratory.

ANIMAL # 1

Eye No. 1

One Macaca fascicularis became available at the University of Western Ontario from another research project. The animal was sedated with Sernolyn and killed by an overdose of Nembutal delivered rapidly by injection. The tissues were treated as Eye 2, 3, 4, and 5.

ANIMAL # 2

Eye # 2 - M31 was treated with (1) focal gallium arsenide (900 nm) exposures of 60 sec. duration, with a total intraocular energy level of 1.32 mJoules per exposure. The laser was a repetitive pulse laser running at 1600 pulses/sec., with an average power of 22 mWatts. These exposures simulated those used by Beatrice et al (1977).
(2) Neodymium laser exposures of 120 m sec. duration and a total intraocular energy of 36 mJ. The eye was enucleated 1 hour after exposure and labelled 2KS.

Eye # 3 - As above, but enucleated 7 days after exposure. This eye was labelled 2KD.

ANIMAL # 3

Eye # 4 - M43 - The entire animal was exposed in a cubicle in such a way that it was looking at a 3/4 m hemisphere, which was illuminated with diffuse argon laser radiation at a wave-length of 514.5 nm. The average radiance of the hemisphere was 10 microwatts per cm. sq. per steradian of source. The pupil diameter of the left eye during exposure and after adaptation was 4.4 mm. and the retinal irradiance was 0.8 microwatts/cm. sq. The animal got a total of 26 hours of exposure in 2 hour sessions, for 13 sessions, over 3 weeks. The whole eye was thus irradiated. The eye was labelled 2JS.

Eye # 5 - The right eye of this animal was patched to prevent the entry of light. This eye acted as a control. We are aware that there is the possibility that some transference of effects from the left eye could conceivably occur, and it is intended later to repeat the experiment using an animal whose eyes are not exposed to any laser irradiation at all, as the control. The eye was labelled 2JD.

The above animals were killed at the Letterman Army Institute of Research, and the tissues were then handled there by Mrs. Karkhanis. The eyes were enucleated immediately, incised at the ora serrata, and immersed in fixative (2.5% glutaraldehyde + 0.5% paraformaldehyde, 0.1M cacodylate buffer, pH 7.4). In slow, progressive stages the cornea, the lens and the vitreous were removed at intervals as fixation proceeded, and when the tissue had hardened sufficiently, in about 30 minutes, the tissues were removed, using a trephine, and fixation was continued for a

total of 1½ hours. The samples were postfixed in 1% buffered osmium, for 1½ hours, and processed through alcohols to Epon 812. The tissue was sectioned on a Reichert OMU2 ultramicrotome, stained in bloc with uranyl acetate and lead citrate and stained again in section, and viewed in an AEI 801 electron microscope. Portions of the retina were cut out with a 1.5 mm trephine. Each trephined portion was numbered and maps of the trephined areas were made, in order to keep track of the exact region of the retina from which a given sample was taken.

The focal gallium arsenide laser irradiances were mapped at the time of exposure in relation to the fine blood vessels. It has proved extremely difficult to locate these in dissection of the material while processing the tissue and a great deal of time was spent trying to find them, then, and also later, in cutting the blocks, as the very low level changes are not readily apparent from thick sections viewed by light microscopy. It has been a most time-consuming operation.

The ages of the monkeys and their histories is unknown.

In conducting the research described in this report the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences, National Research Council.

Thick sections (usually 1μ) were cut from all samples, stained with 1% toluidine blue + 0.25% sodium borate and photographed on Panatomic X film in a Zeiss "Universal R" Research Microscopic.

RESULTS

Eye # 1

Normal Retina. Macaca fascicularis.

This tissue displayed the following points of interest:

Bruch's membrane contains some of the densitites associated with normal aging (Hogan et al., 1971) and the endothelium of the choriocapillaris is thin and fenestrated (Fig. 1), as is normally the case.

The pigment epithelium appears normal with well-developed basal infoldings with clear spaces, and small basal mitochondria. The rough endoplasmic reticulum (RER) is apical while the smooth endoplasmic reticulum (SER) is evenly distributed and does not show any irregularities such as clumping or pinching as described by Kuwabara (1979) in retinas exposed to light insult. The melanin granules are of two kinds: (1) elongated, at the cell apex, and especially in the long microvilli, and (2) round granules found in the cell body. Many phagosomes containing outer segment discs are present. The rod outer segments reach all the way to the apical cell surface or they are very close to it. The apical surface of the PE is smooth and even. The pigment epithelial cell nucleus is sometimes somewhat scalloped in outline (Fig. 1), but is usually round.

All the layers are well preserved and Fig. 2 shows the inner limiting membrane (ILM). Some vitreal condensations are present on it. The dark Müller cells (MC) with its "pegs" into the basement membrane

and the neurotubule - filled axons of the nerve fibre layer, separated by extensions of the MÜller cells, are well-displayed.

It is interesting to note that unlike most of the published pictures, the two centrioles at the apex of the rod inner segment are not close together. This is an observation made several times in this study (see later). 'Shredded' or 'embryonic' melanosomes are present.

Other control samples are described with the eyes from which they were taken.

Eye # 2 - M31 (2KS)

The eye was enucleated one hour after irradiation by gallium arsenide laser.

Mrs. Karkhanis and Mr. Smith have diligently sectioned the material of the eyes M31 looking for lesions. The process has been immensely time-consuming and rather depressing for the technicians. Blocks were sectioned and 1μ thick sections were examined at maximum intervals of 20 μ to try to locate some subtle changes. In 2KS # 4, e.g. nothing was located to indicate a lesion except for one pigment epithelial cell which was light staining. Other blocks, e.g. 2KS, areas 2 and 3, were also examined very carefully by transmission electron microscopy and some subtle changes are reported which might be a result of the laser irradiation. It is suggested that much more detailed mapping with surrounding marker burns be used in the future to delineate the regions of our concern so that it will be practicable to section a

discrete area for thorough TEM examination.

Descriptions of specific areas of the 2KS eye follow:

A detailed description is given of area 2KS6 (peripheral retina) as it covers a good deal of what was seen in all the other peripheral areas, including those with lesions.

A. Area of lesions 8, 9 (2KS6)

(i) Light Microscopy

The only unusual features seen were a slight dip in the middle limiting membrane (MLM), and an 'aberrant' nucleus beside a pedicle.

This latter was seen, very infrequently,but in other eyes also, and therefore cannot be considered to be the result of laser irradiation. The cone outer segments (COS) are dark-staining and have knobbled outlines. This is also seen in other retinas. In the 2J retinas (which appear with coagulated cytoplasm) this is seen rarely, but it is common in all areas of the 2K eyes. These nodular excrescences on the COS have been illustrated elsewhere (Borwein, 1981; Steinberg and Wood, 1979). They may be the result of aging (Marshall et al, 1979), or an unknown pathology in this monkey.

(ii) Transmission electron microscopy (Area 2KS of lesions 8, 9)

The pigment epithelium (PE) contains the usual organelles, and a few unusual ones. These are:

(a) a few large melanosomes which appear "embryonic" or "shredded" (Fig. 3) (Kuwabara 1979). Kuwabara (1979) described similar melanosomes in retinas exposed to photic insult. They closely resemble melanosomes in the fetal eye but are larger. However, these were seen in other non-irradiated areas of this retina and in other eyes. If they are indicators at all, then their incidence may be indicative of the degree of laser impact.

(b) The dark cytoplasm contains abundant smooth endoplasmic reticulum (SER) and some SER vesicles appear clustered and "pinched" together (Fig. 3). Again, Kuwabara (1979) ascribes this to the effects of photic insult, but these are also seen in other retinal areas not subjected to laser irradiation. It may be important only if it can be shown that the incidence of "pinched" SER profiles increases with light-insult.

(c) Elongated structures which contain membranes oriented parallel to their long surfaces. They are arranged in groups, most often parallel to each other and to the lateral cell margin with which they are always closely associated. Sometimes they appear in concentric circles. They appear to be mitochondria and are often more than half the height of the PE cell. They are present in addition to the small mitochondria found in the basal part of the cell. They are seen in the PE of all the four eyes examined (K and J series) and are, therefore, not a result of light-treatment (e.g. see Figs. 26, 36).

(d) A small striated rootlet was seen, very rarely, in the apical part of the PE cell.

(e) The basal infolds are not very large or conspicuous.

There are many complex melano-lipofuscin bodies, and some small residual bodies in the PE (Fig. 3). Hemidesmosomes on the PE - Bruch's membrane border stain clearly (Fig. 3). In some places the PE microvilli seemed to be sparse and less well-developed. This is sometimes associated with a laser-irradiation effect.

Cone phagosomes are seen in the PE microvillous processes, and phagosomes are also seen within the PE cell body.

The rod outer segments (ROS) reach to the PE cell body. The ROS show some convolutions (Fig. 4) (Borwein et al 1977; Marshall et al 1979; Borwein 1981) in which the discs themselves are normal (Fig. 5). Some ROS show differential staining of the discs. The cone outer segments (COS), however, are very disturbed. Their discs are pyknotic and grouped in strange configurations. There seems to be a larger component of cytoplasm associated with the COS compared with the ROS (Fig. 4). As will be discussed later, the ciliary backbone is much better developed in the COS. Similar COS were seen in other areas of the 2KS eyes. ROS convolutions are known to increase in frequency with age (Marshall et al 1979) and the disturbed COS may also be a consequence of aging.

The inner segments contain reasonably well-preserved mitochondria. The rod inner segments contain dilated cisternae of the SER. Striated rootlets are seen in most rod inner segments (Fig. 6), but only rarely in the nonfoveal cone inner segments. Rootlets are seen often in the foveal cones. They often appear to be multi-striated. The abundant mitochondria of the cone ellipsoid may hinder the visualization of the striated rootlets. Monkey cone striated rootlets have been reported but

as less often seen and less well-developed (Murray et al 1973) than those of the rods. In the literature the striated rootlet has been regarded as an organelle of the rods only.

The two centrioles of the inner segment are always widely separated (2-2.6 μ). This is a novel observation. In the published micrographs the two centrioles lie in close proximity. The striated rootlets appear to arise independently from each centriole.

In the Müller cells (MC), very close to the external limiting membrane (ELM), there are present 2 centrioles, as reported previously by Borwein et al (1980). These are surrounded by a group of small, densely-staining bodies of irregular outline which I shall call 'satellite bodies' and which are seen in this position whether the centrioles can be seen or not. In addition, there are electron-dense bodies and myelin figures seen in the Müller cell cytoplasm in the ONL (illustrated later, Figs. 15, 15A).

There are a few pyknotic nuclei seen in the outer nuclear layer (ONL),and the inner nuclear layer (INL) now and then, and some small dense bodies in the Henle layer and in the outer plexiform layer (OPL).

The pedicles usually stain homogeneously, but some contain very enlarged mitochondria, the cristae of which are disturbed, and there are a few pedicles that are pyknotic (except for the mitochondria) (Fig. 7). There are some cystic spaces in the spherules and there is one pyknotic fiber in the Henle fiber layer (Fig. 7). One pedicle is missing entirely and the space it left is filled with a vague coagulant and some myelin figures. The neighbouring pedicle contains a 'tubule-complex' (Fig. 8). The

'tubule-complex' is a cluster of microtubules seen very frequently in the pedicles and spherules of both the 2J and 2K eyes. Convoluted tubular structures in monkey retinal receptor terminals have been described by Glees and Spoerri (1977) who thought they were connected to the vesicles surrounding the synaptic ribbon. They reported that microtubules occur generally in the terminals but are very labile and easily destroyed by fixation. The "tubule-complex" is illustrated in Fig. 9 and the synaptic vesicles of the pedicle can be seen.

In the INL there are deeply staining nuclei which are probably those of the MUller cells. In the cytoplasm at one or both ends of the nucleus frequently there can be seen parallel arrays of rough endoplasmic reticulum. This is seen in all the retinas of the 2K and 2J series. (Fig. 10). This is not apparent in the published micrographs in the literature.

It is commonly seen that there are cystic spaces of varying sizes in the ganglion cell layer (GCL), the nerve fibre layer (NFL) and in the inner plexiform layer (IPL). These spaces are both inter- and intracellular, the MUller cells being most often affected.

The ganglion cell contains a large nucleus with a very distinct nucleolus, the pars amorpha of which is clearly displayed. There are swollen mitochondria with disrupted cristae present in some GC.

While the lesions were not located with assurance, there are a few indicators of possible laser-induced abnormalities present in the pigment epithelium, in the few pyknotic nuclei, Henle fibers and pedicles, and in the MUller cells (edema).

B.

Peripheral areas without any lesions were examined and found to closely resemble the description given for the area 2KS6.

The pigment epithelium contains lipoidal globules, elongated mitochondria as well as the usual small mitochondria, and the rod outer segments reach to the pigment epithelial cells. Profiles of "pinched" SER are plentiful. It is therefore clear that this appearance of the SER is not the result of irradiation. The ELM is not very conspicuous and there are many electron dense bodies in the Müller cell processes of the ONL.

C. The Macula (including the fovea) (M31 - 2KS)

There was no lesion in the macular region itself. The macular area was extensively investigated and the area is described below for comparison with the eyes that were patched or exposed to whole eye argon irradiation (2J series).

(i) Light microscopy

The fovealar area contains some inner segments which stain more densely. The long thin outer segments of the foveolar cones are uneven and knobbled (as they are in the entire macula). They reach to the pigment epithelium. The foveolar pit has steep sides. The nuclei of the foveolar cones are distant from the ELM (Fig. 11). The foveal cones

reach to the PE, while the extrafoveolar cones do not. In the periphery the ROS reach to the PE.

(ii) Transmission electron microscopy

The appearance of Bruch's membrane is as illustrated in Fig. 1.

The pigment epithelium contains smaller cells than those of the periphery. Many round nuclei are visible. The elongated mitochondria are not as long in comparison to the length of the cell, as they are in the periphery. Profiles of "pinched" SER are plentiful. Many cone phagosomes can be seen in microvillous processes. Foveolar cones reach to the apical border of the PE. Many large 'embryonic'-type melanosomes are present (Figs. 12, 13). The basal infoldings have clear spaces between them, and they create a light-staining border in the PE. Small, round lipid-like globules are present either in clusters, or scattered (Figs. 12, 13). Small electron-dense bodies are sometimes seen between the PE cells at their lateral borders.

The cone outer segments have very uneven outlines. The discs stain deeply and there are many 'knobs' of distorted cones, (Fig. 12), the discs often being in whorled configuration. The most distal parts of both the cone and especially the rod outer segments are usually not distorted.

The cilium of the foveolar cone is longer than that of the peripheral cones. The two centrioles of the apical inner segment are close together (usually .13 - .2 μ apart). Striated rootlets are seen in the foveal and foveolar cones and in the rods of the fovea, but the cone striated rootlet usually seems to be thinner and much less conspicuous

than that of the rods (Fig. 14). There are no mitochondria at the apex of the foveolar cone inner segment. The microbutules and the ribosomes of the inner segment are well-preserved. The inner segments are sometimes seen to contact each other over short distances (on both sides of the ELM) and these contacts are seen also at the level immediately scleral to the MC microvillous border.

The ELM is very well-developed. There are many long fibrils associated with the plaques of the desmosomes than comprise the ELM (Fig. 15).

The Müller cells of the foveal region contain many inclusion bodies, near the ELM, and in the ONL generally. The foveolar inner segments contain autophagic vacuoles, vitreal to the ELM. The Müller cell processes in this region contain very electron-dense bodies and other inclusions. These and other less densely staining inclusion bodies, the centrioles of the MC and their surrounding "satellite bodies", can be seen in Figs. 15, 15a.

Homogeneously electron-dense bodies, closely resembling those seen in the MC, are seen also in the cone inner segments in autophagic vacuoles. Inclusion bodies of the MC are seen continuous with the plasma membrane of the MC, close to the inner segment and knobs of the inner segment project into the MC (Fig. 15A). It is suggested that MC may receive undigested residues expelled from the inner segment autophagic vacuoles. In Figs. 15a it can be seen that, near the well-developed ELM, the MC contains a centriole, "satellite-bodies" and a membranous inclusion body. Frequently a thin striated rootlet is seen here also.

One pyknotic cone nucleus, containing much heterochromation, was seen at the ELM in the macula. This is reported only because an isolated pyknotic nucleus may be found in all parts of the retina in normal tissue. The pedicles contain one or more clusters of the "tubule-complex". A few have very enlarged mitochondria. One large nucleus is seen lying alongside the pedicles on the scleral side. A large cystic space was seen the size of, and in the position normally occupied by, a pedicle.

The ILM is very thin in the fovea, with a very uneven outline. The thin MUller cell processes that approach the basal lamina form a very complex pattern of interdigitations.

D.

In Area No. 8 one zone was found which was normal in most respects but the apical border of the pigment epithelium was slightly scalloped and the microvilli contained few or no melanin granules. The pigment epithelium contained the organelles described above and the nuclei were circular and normal looking.

There were a few rod outer segments present, the outer segment discs of which were in disorder and in longitudinal array at their distal ends which is a unique finding in this study, as the ROS distal portions remain intact even when there are convolutions in their mid-zones. This might perhaps be the area of lesion # 10 (Fig. 16).

E. Gallium arsenide lesions

Block # 4, containing lesions 5, 6, and 7 was sectioned in its entirety by 1 μ sections, and examined by light microscopy. In groups of serial sections there were seen one, or two neighbouring, cells in the PE that failed to stain with toluidine blue and presented as a clear space with dark melanin granules and microvilli with melanin granules (Fig. 16A). This was all that could be attributed to laser irradiation. Blocks 2 and 3 were sectioned by 1 μ thick sections in the areas in which the lesions were mapped. The lesions were not located. By TEM, all that was seen was a pocket of MUller cell edema in the ONL.

Eye # 3 - M31. 2KD.

A. The control areas

(i) Light Microscopy

The retina appears normal except that there are a number of cystic spaces below the ILM. This is not an unusual finding in normal retinas.

(ii) Transmission electron microscopy

Bruch's membrane is normal, and contains some dark areas such as is seen in aging retinas. The pigment epithelium has a dense cytoplasm in which "pinched" SER profiles are seen. The basal infolds are wide and clear and resemble that of the fascicularis monkey (Fig. 1). Otherwise the pigment epithelium resembles that of the 2KS eye.

The rod outer segments reach to the apical border of the PE cells. While many of the ROS appear normal, there are some that bear nodules of re-arranged discs (Fig. 17) in their mid-regions. The cone outer segments are very dark staining and their discs are rarely in regular stacked array. Because the COS discs are in disarray the considerable cytoplasmic component of the COS becomes apparent (Fig. 17).

The inner segments are similar to those of the 2KS eye. Autophagic vacuoles are common and some contain electron-dense inclusions which closely resembles structures seen in the Müller cell cytoplasmic processes of this region (Fig. 15). There are small, extracellular cystic spaces around the innermost cells of the INL, as are often seen in published photo-micrographs of normal tissue. In general the inner retinal layers resemble those of the 2KS eye. The ILM has a thick basement membrane. The dark MC processes approach the vitreous surface in columns which fan out to form the ILM. The nerve fibre layer is well-preserved; but nevertheless, it contains a few cystic spaces.

B. Neodymium laser irradiations

(i) Light microscopy

The overall shape of the lesion can be seen in the thick sections. The pigment epithelium is artefactually detached. It is markedly scalloped and cells lie free, close to it (Fig. 18). The inner and outer segments are absent from the lesion center in which the external limiting membrane

cannot be seen clearly. The pyknotic nuclei of the lesion center in the ONL appear to be in a cluster and they are widely separated from each other. The ONL shows considerable edema. Pyknotic nuclei in the INL, nearest to the OPL, are probably horizontal cells (Fig. 18, 19). They do not lie immediately beneath the pyknotic nuclei of the ONL, but are displaced to one side of it and the inner fibers connecting the pyknotic nuclei of the ONL to the synaptic terminals are affected and appear as a light band at an angle to the retinal layers (Fig. 18). The wider area of PE disturbance and the displacement are described by Marshall et al (1975) in ruby and argon laser lesions in primate retinas. The OPL is a little cystic and the GCL is markedly edematous (Fig. 18) and there is some vacuolization in the IPL. The PE cells are often hypopigmented beneath the marked scallops and there are several free cells near the PE in the subretinal space.

(ii) Transmission Electron Microscopy

The material is well fixed by conventional standards. Bruch's membrane is thickened and contains cells with nuclei, which may be pericytes or fibroblasts.

The pigment epithelium has a very scalloped apical margin over an area considerably wider than the lesion area in the retina itself. It contains many irregularly-shaped nuclei. Free cells lie in the subretinal space. Melanin granules tend to be apical in position, but there are only a very few melanin granules in the microvilli of the scallops, and the regions between the scallops (Fig. 20).

Melanin granules are located in the cell body and only rarely in the microvilli. There are no "embryonic-like" melanosomes, ascribed to light-damage (Kuwabara 1979). There are areas of hypopigmentation, areas showing very dense cytoplasm and many clusters of melanin and/or lipofuscin bodies. Lipid-like globules are seen in the PE cells (Fig. 21) and also in the free cells. There are also melanin granules, phagosomes with OS discs, and lipofuscin granules present in the free cells (Figs. 20, 21). The degree of scalloping varies so that a sequence can be seen from barely scalloped to a scallop with a pinched neck-like basal attachment to the PE, all of which suggests that the PE is the source of the free cells. The scalloped regions bear many long microvilli devoid of melanin granules, and the basal infolds are very reduced under these areas. There are abundant dense bodies in the parts of the PE towards the edge of the lesion.

The PE cell has reduced basal infoldings; a large number of pale lobulated nuclei (no round ones are seen); many (and long) profiles of "pinched" SER; lipid-like globules, normal mitochondria, and RER in both an apical and a basal (atypical) position. The hemidesmosomes do not stain well and it seems they may not be present which might suggest that these cells are not as firmly attached to the basement membrane as in normal. Generally the cytoplasm is very dense. No elongated mitochondria in parallel arrays at the lateral cell borders are seen.

There is an elaborately invaginated lateral margin connection which appears to be filled with basement membrane material (Fig. 21).

The ELM is present even when there are no rods or cones left. The attachments seem then to be between neighbouring MUller cells, the microvilli of which are very prominent. The ELM seems to form a retinal boundary (Fig. 22).

In the lesion center only fragments of the IS and OS can be seen in the subretinal space in various stages of degeneration. The inner segments near the lesion center are club-like (Fig. 22) or very truncated. Some contain mitochondria. Some attach to other inner segment stumps (Fig. 23). Marshall et al (1975) discuss the tendency to membrane fusion in laser irradiated retinas. At the edge of the lesion the inner segments of rods and cones contact each other by small papillae. Striated rootlets can be seen in these rods.

The nuclei of the ONL are in varying stages of pyknotic degeneration (Figs. 23, 24), as is their surrounding cytoplasm, and some nuclei are missing (Fig. 23). There is considerable edema. Only the most advanced stages of disintegration can be seen by light microscopy (Figs. 18, 19).

Only those cells of the INL that are nearest the OPL show severe degenerative changes, with very pyknotic nuclei, or nuclei totally destroyed, and pyknotic cytoplasm with enlarged disorganized mitochondria. It is interesting that the mitochondria swell and undergo disintegration while the surrounding cytoplasm becomes pyknotic (Fig. 25).

The Muller cell processes in the lesion center in the ONL are very pale. They contain a good deal of debris (Fig. 23); and there is a considerable amount of edema. Pyknotic and degenerating bodies can be seen in the Henle fiber layer (Fig. 25). This is the layer that by light microscopy appears only as a light streak (Figs. 18, 19).

Degeneration of the photoreceptor synaptic terminals seen faintly by light microscopy (Figs. 18, 19) can be seen clearly in Fig. 25. The terminals are either shrunken, or electron-dense, or cystic, or devoid of contents or in various combinations of all of these. At the edges of the lesion the changes in the synaptic terminals become gradually less marked and they appear to be normal and the tubule-complex is present.

A nucleus is seen lying alongside the synaptic terminals. It may be a displaced nucleus from the ONL and is found very infrequently in all regions of the retina.

There are cystic spaces, largely in the Müller cells, in the IPL, the GCL and to a lesser extent in the NFL. The Müller cell is very edematous throughout the retina, but the degree of edema varies in different parts of this extended cell. Cystic spaces are present under the ILM.

Away from the immediate area of the lesion the retina becomes more normal in appearance. The pedicles contain large mitochondria and the tubule-complex, as reported elsewhere in this report (Figs. 7, 8, 9). The nuclear layers are normal. The inner segments contain mitochondria, striated rootlets, and microbutules. Outer segments are distorted in their mid-zones, in the same way that was seen before (Figs. 5, 17), but the frequency of these distortions and their extent especially in the rods is greater, and, again, the cones are most severely affected. The rods have discs that stain with differing electron-densities. There are no, or hardly any, vesicular or tubular figures in the discs such as were seen by Marshall (1975), but rather whorls of electron-dense discs, and other re-arrangements of the discs within the outer segments. The distal ends of

the outer segments contain the normal orderly disc stacks. It is the proximal, and especially the mid-zones, that are most affected. Vesiculo-tubular breakdown of discs has been regarded as a sign of greater damage than are whorled discs (Adams et al, 1972; Marshall et al, 1975) and the differential staining of the discs may be a sign of minimal injury. The rod discs usually stain uniformly.

In this area there is an elongated nucleus (not pyknotic) lying immediately below the ILM, near a pocket of cystic spaces. Such spaces occur at intervals in this zone, but the nucleus here is a unique finding.

While the laser-damaged area forms a discrete area there is nevertheless a small transition area from affected to normal tissues with small cell changes, and there is the displacement phenomenon described above. The change from affected to normal cells is more sharply demarcated in the pigment epithelium than it is in the rest of the retina. Marshall et al (1975) described argon and ruby laser lesions of the primate retina. The neodymium laser lesion in this study matches more closely the kind of changes they reported for the argon laser, but the changes found here are milder than they reported.

Gallium arsenide Lesions

Block 4 has not yet been sectioned. Lesions in other blocks were not located with any degree of certainty. Small aberrations, sometimes ascribed to the effects of photic-insult, were seen throughout the retina. It is possible that very slight alterations are corrected within 7 days and that changes need to be assessed not for presence-or-absence, but for frequency and intensity. Our new Zeiss Videoplan Digital Image Analyser will be used in the current investigation. In some 'lesion' areas all that could be seen that seemed different was a greater MC edema.

Eyes M43, # 4, # 5

(2JD, patched; and 2JS, whole eye exposed to argon irradiation)

Comment on the fixation

The general appearance of the tissues suggests that they are not well fixed, for reasons which seem inexplicable. The 2K retinas took much longer to cut up during the fixation process as locating the lesion areas was a problem, and yet these eyes have well-preserved membranes. In the 2J retinas there is consistently a flocculent, coagulated, and/or granular look to the cytoplasm, and the plasma membranes are either poorly preserved, indistinct, or absent. Sometimes the tissue failed to take up the stain. Marshall et al (1975) reported severe coagulation effects on retinal cells of argon-treated eyes. In this experiment, both the exposed and the patched eye showed the same coagulation granularity so that it is not possible to ascribe it to the treatment unless a carry-over effect to the patched eye is postulated. The methods of fixation are identical with those which have routinely produced good results in our labs.

Convoluted and distorted (knobbled) outer segments are frequently said by some to result from poor fixation but they are rarely seen in the 2J eyes and frequently seen in the 2K eyes. Also, the pigment epithelium is reasonably well fixed. The previous history and the age of this animal is not known to the author. Had it, for example, been subjected to excessive light exposures in the past? In the 2K animal where there are considerable convolutions and distortions of the outer segments, this might well be due to the greater age of this animal (Marshall et al 1979).

Eye # 4 M43 2JS The whole eye exposed to cumulative argon laser irradiation.

All the regions numbered on the original map made when the eyes were fixed were separately investigated and evaluated. For purposes of description the eyes have been divided into different regions, so that the differences can be emphasised.

Light Microscopy

Fig. 43 illustrates the degenerative changes seen in the thick sections. The ONL contains many pyknotic nuclei. Pyknotic nuclei are rare in the INL and the GCL. Pyknotic necrotic rod inner segments, rod inner and outer fibres, and spherules can be seen and also the large cystic spaces of the rod inner segments.
The full extent of the degenerative changes is seen by TEM.

Transmission Electron Microscopy

A. Peripheral regions

Although there are some differences between different parts of the peripheral retina, the similarities are great, and the differences relatively small.

The endothelium of the choriocapillaris is thickened in places. The hemidesmosomes stain clearly. The basal infoldings of the pigment epithelium are often short, and not very clearly displayed. The elongated mitochondria described in the other eyes are also present here, usually in approximately parallel arrays but sometimes in whorled patterns (Fig. 36).

There are many small,dark-staining bodies especially near the basal infoldings (Figs. 36, 37). In a few photomicrographs striated rootlets are seen at the apex of the pigment epithelium. They were not seen here as regularly and as frequently as reported by Schuscheereba et al (1981). They found that in eyes exposed to argon irradiation in the same way as eye 2JS that the number of striated rootlets and centrioles in the apex of the PE cells was 2.5 times the number seen in the patched eyes. Large "embryonic-type" melanin granules were seen (Fig. 36). Long melanin granules, usually seen in the microvilli, are also seen in the cell body in small numbers. The apical surface of the PE bears some hump-like projections from which arise a cluster of microvilli. In the most peripheral regions the apical PE surface is sometimes slightly undulating or scalloped, which is normal. Large phagosomes are present but they are not abundant. Profiles of "pinched" SER, reported by Kuwabara (1979) to form as a result of photic insult, are infrequently seen. The cytoplasm appears dense and tends to stain darkly, and there is an abundance of ribosomes (Figs. 35, 36, 37).

In an area near the macula there is seen a complex interdigitation, (containing basement membrane material),of the mid-zone of the lateral borders of the cell. Basement membrane material is seen in some of the spaces of the basal infoldings. This was not seen in the other eyes. At the pigment epithelium - Bruch's membrane interface there is seen a structure resembling a druse (Fig. 37) in which are a number of cystic and electron-dense inclusions.

Some outer segments in the most peripheral areas reach to the pigment epithelium, and also in two regions immediately temporal to the macular area. For the most part, the rod outer segments of the argon irradiated eye reach only towards the edge of the microvillus border (Fig.38) whereas in the patched eye a preponderance of the rods can be seen lying appressed to the apical edge of PE cell body itself

The ROS discs do not stain crisply. They are granular and the plasma membranes are not preserved. For the most part their discs are in orderly array and only a very few are convoluted or knobbled. The great majority of ROS have uniformly staining discs. Some are so poorly preserved (in the most peripheral area examined) that the discs are barely distinguishable. In some places some of the discs, in orderly array, have dark staining pyknotic condensations at their edges (Fig. 39). There are a few ROS which show some discs in whorls, and a few cones show some vesiculation of the proximal discs, and uneven staining (Fig. 40), associated with the necrosis and pyknosis described below.

The inner segment centrioles are (0.7 - 1.4 μ) apart from each other as they are in the 2KS eyes series (whereas is in the fovea they are very close together, 0.2 - 0.3 μ apart). The cilia, centrioles, striated rootlets, and ribosomes stain deeply. The striated rootlets are seen in most rods in Fig. 41, and one can be seen traversing the cystic spaces near the ELM, supported by threads of cytoplasm. The striated rootlets, which appear so frequently, were not counted as it is not clear whether there is one broad undulating striated rootlet in each inner segment which may look like separate rootlets in longitudinal section, or whether there are several separate striated

rootlets in each inner segment. However, the impression gained is that striated rootlets are especially abundant in this retina. Striated rootlets are also seen in the foveolar cones but seemingly less well-developed than in the rods. Striated rootlets are seen also in MUller cells, near the ELM, in association with a pair of centrioles, but this rootlet is very thin and does not stain boldly. The function of striated rootlets is not known. It is not known whether or not they are constant or dynamic organelles; nor whether the striated rootlets of the PE, the IS, and the MC are all identical. They need to be carefully assessed in differing light regimens and in the dark. Schuscheereba et al (1981) found more PE striated rootlets in light exposed retinas compared to occluded eyes.

The inner segments contain cystic spaces, especially in the rods, scleral to the ELM (Fig. 41). The mitochondria of the ellipsoid are sometimes swollen and often vaguely defined (Fig. 40). Some inner segments contain so much coagulated material that only microtubules and striated rootlets are clearly seen, and sometimes only the latter (Fig. 40).

Notwithstanding, the general cell-outline and the contained cystic-space (when present) are clearly disernible.

In general the CIS is much better preserved than the RIS. The rods are more affected in general by degenerative changes and necrotic rods are seen, especially in the most temporally peripheral zone examined, but also in a region immediately below the macular area and in a small patch near the macula itself. In these affected areas in the ONL, and to a lesser extent in the INL, there are nuclei in varying stages of pyknosis, and where

the nuclear pyknosis is intense the cytoplasm is also pyknotic with surrounding edema. The associated rod inner segments and inner and outer fibres, are also necrotic, and some spherules show clear cystic spaces, shrinkage and varying degrees of pyknosis (Figs. 42, 44). Fig. 43 is a light micrograph displaying the cystic spaces of the inner segments and some pyknotic RIS, nuclei in the ONL, inner and outer fibers and spherules. In a portion of the block containing the macula a degenerating patch is seen, displaying considerable edema, with pyknotic and missing nuclei and cystic spaces in the inner segments (Fig. 45). The pedicles are homogeneously stained, and a few have enlarged mitochondria, and when, rarely, a dark-staining pedicle is seen it is never as dark as the necrotic spherules.

The Müller cell cytoplasm in the ONL is very pale staining, edematous and contains very few inclusions. Müller cells are frequently seen to contain a pair of centrioles immediately vitreal to the ELM, associated with which one occasionally sees a thin striated rootlet staining lightly, and a collection of small irregular dark staining bodies, the "satellite" bodies.

There is an occasional pyknotic cell in the ganglion cell layer and some of the ganglion cells contain expanded SER profiles or slightly swollen mitochondria, and glycogen particles (Fig. 46).

The synaptic ribbons are found to be shorter in the spherules of this eye compared to those of the patched eye. This is discussed on p. 38.

B. The Macular area, including the fovea

This area was explored in great detail. The findings are summarised below, with emphasis on the differences.

The most consistent and probably the most significant finding for the whole eye exposed to argon irradiation is the distance of the outer segments from the pigment epithelial apical cell border compared to the patched eye.

The PE basal infoldings are well developed and the spaces are clear and wide. There are many groups of long mitochondria in approximately parallel array which underlie the lateral cell border in the basal half of the cell and they extend for more than half of the height of the cell. Sometimes these mitochondria are seen in concentric arrangements (Figs. 48, 49). Clusters of small globules with homogeneously stained contents and a narrow irregular dark border are present in the foveolar PE. These may be lipid droplets or lysosomes (Fig. 50). The microvilli are long and carry many elongated melanin granules (Figs. 48, 49). "Embryonic-like" large melanin granules are present (as seen e.g. in Fig. 36).

The rod outer segments do not often display convolutions. The cone discs are generally in orderly array but some COS have convoluted outer segments in which the discs themselves are normal (Fig. 51). In some the discs may be separated from each other slightly, in small groups (Fig. 52) and some discs within one COS may stain darkly while others stain lightly (Fig. 51).

The inner segment ellipsoids have many very swollen mitochondria (Figs. 51, 53), in which the cristae are disorganised and they contain only some flocculent material (Fig. 53). The most distal part of the CIS does

not contain mitochondria. Striated rootlets and microtubules are often seen, as well as a pair of centrioles very close together. Calycal processes arise from the distal end of the inner segment (Fig. 53). CIS make contact with each other by small protuberances (Fig. 54). The CIS is wider at the ELM and tapers towards the COS (Fig. 54).

The ELM is very conspicuous as it stains boldly. The fibrils and the plaques of the desmosomes are very well-developed (Fig. 55).

A few pyknotic rod nuclei are seen and there are scattered pyknotic nuclei in the INL and a rare pyknotic nucleus in the GCL.

The MC processes in the ONL, near the ELM, contain centrioles, clusters of satellite bodies. A few microtubules and occasionally a thin striated rootlet is seen. Electron-dense inclusion bodies and myelin-figures of whorled membranes which are so commonly seen in the 2K eyes, are not seen here (Figs. 55, 56).

C. The Fovea

Light Microscopy

The pigment epithelium displays the normal polarity. There are many elongated melanosomes in the long microvilli. The elongated outer segments reach only as far as the microvillus border of the pigment epithelium. The inner segments contain very enlarged mitochondria. The ELM is very clearly displayed and the foveolar dip is apparent. The space seen in the ONL in the photomicrograph is a tear created in tissue-processing (Fig. 47).

Transmission electron microscopy

Bruch's membrane is essentially normal. It contains some vacuolar spaces. The endothelium is thin and fenestrated.

The pigment epithelium bears long thin microvilli in which are found elongated melanosomes (Fig. 48, 49). "Embryonic" melanosomes are present in small numbers (Fig. 48). Clusters of lipid-like globules, each homogeneous and with a dark border, are found in the basal part of the cell, and rarely, in a microvillus. Many large, complex melanin-lipofusion bodies are seen (Fig. 50). There are many elongated mitochondria grouped in approximately parallel arrays, alongside the lateral cell borders, and often extending for more than half the height of this tall cell (Figs.48, 49). The hemidesmosomes stain well. The basal infolds are well developed. Phagosomes are seen infrequently. This is expected as cones are known to shed their discs after the onset of the dark period (for a review of this topic see Borwein, 1980). Some nuclei are irregular in outline and have clumped heterochromatin (Fig. 50).

The cone outer segments, and the ROS of the fovea (Borwein et al, 1980) do not reach to the apical border of the pigment epithelium, except very rarely. They end near the tips of the microvillous border (Figs. 48, 49).

The very long COS are for the most part in ordered array but there are some convolutions, especially in the mid-regions (Fig. 51). The ciliary backbone is prominently displayed and sometimes a dark rodlike structure is seen in it alongside the outersegment discs (Fig. 52). In a few cones the discs stain unevenly. Calycal processes are seen. (Fig. 51, 53).

The cone inner segment is, like the outer segment, very long and thin. The apex is often devoid of mitochondria as has been reported before (Borwein et al, 1980). The mitochondria of the ellipsoid are swollen and often so altered that the cristae are not distinguishable (Fig. 51). The two centrioles are close together (0.2 - 0.3 μ apart) (Fig. 53). The long cilium of the foveolar cones and the two centrioles stain very darkly. There are striated rootlets in the foveolar cones (Fig. 53) but they do not seem to be as well developed as are those of the rods. In any one section several separate strands may be seen. The microtubules of the inner segment and of the Henle fibers are well preserved. The outer segments bear small knob-like protrusions that contact those of neighbouring cones immediately scleral to the apical edge of the Müller cell microvilli (Fig. 54). In the myoid there are many autophagic vacuoles, and small vacuolar spaces, abundant ribosomes, microtubules, and Golgi bodies Near the ELM the inner segments are broader and they are very close together (Fig. 54).

The ELM stands out boldly, as it stains deeply. The fibrils of the desmosomes seem to be better developed in the foveal region than elsewhere (Fig. 55).

The Müller cells in general resemble those of the macular area. The satellite bodies are often seen (Fig. 56).

Pyknotic nuclei, or nuclei with large clumps of heterochromatin are seen in the ONL.

The basement membrane of the ILM is very thin and the thin Müller cell processes can be seen in the basement membrane in the fovea and the macula.

Cone synaptic ribbons measure 0.3 - 0.4 μ and rod synaptic ribbons range from 0.9 - 1.5 μ with most measuring 1.4 - 1.5 μ .

Eye # 5 - 2JD - Patched Eye M43

All the trephined areas were sampled. Unfortunately, the foveolar part of block # 6 was accidentally destroyed while the block was being trimmed, but the parafovea and the edge of the fovea were examined. Most of the areas showed similar features, and these will be described together. Areas 9 and 4 showed interesting differences and they are described separately. Area 9 is a region nasal to the optic disk and area 4 is the most temporally peripheral region examined.

All areas except zones 9 and 4:

(i) Light microscopy

The ELM stains boldly. One necrotic synaptic terminal can be seen. There is some edema in the ONL. Some small clear spaces can be seen in the rod inner segment near the ELM.

(ii) Transmission electron microscopy

The electron micrographs display the granular, coagulated, flocculent appearance of the cytoplasm and some cellular structures, and the poor preservation of the membranes, the extent of which is not indicated in the light micrographs.

Bruch's membrane is normal and contains some scattered dense-staining inclusions, and it sometimes contains small vacuoles. The endothelium of the choriocapillaris is well preserved and the fenestrations are visible.

The pigment epithelium has an essentially even apical border. There are groups of aligned, very elongated mitochondria associated with

the lateral cell border (Figs. 26, 36, 38, ~~and 8~~) as has been seen also in 2JS and 2K series. The usual small mitochondria occupy a basal position and the spherical melanin granules are seen in the apical part of the cell, while the large, long melanin granules are found in the long microvillous processes, as is normally the case. A few lipid-like globules are seen, and also rarely, in a microvillus. There are relatively few complex melanin-lipofuscin bodies, compared to both the 2K series and eye 2JS. The basal infoldings do not appear to be very well-developed but the hemidesmosomes at Bruch's membrane stain deeply.

The discs of the rod outer segments are in the normal orderly stacked array and the ROS reach all the way to the PE apical cell border and are seen appressed to its membrane (Fig. 26).

The ROS stain uniformly. There are only a very few convoluted ROS and in these the discs are in the normal stacked array. The COS are either very dark-staining and display a prominent ciliary backbone, or the discs stain unevenly, some lightly, and some darkly. Especially at the basal end of the COS there are sometimes seen a few vesicular profiles (Fig. 27). The cilium stains very darkly, and so do the ciliary microtubules that extend alongside the outer segment.

The cytoplasm of the inner segment shows considerable coagulation. It frequently looks very granular. Sometimes the mitochondria can be distinguished and some are swollen, but the frequency and extent of swelling is far less than in the 2JS eye. Microtubules and striated rootlets can be seen in almost all the rods, all the way to the nuclear area and the two centrioles are not close together (about 1.8 μ apart). The inner segments extend

distally to form calycal processes around the proximal inner segment.

The ELM stains darkly. The rod inner segment myoids often show large cystic spaces of varying sizes, some containing flocculent material (Figs. 28, 29) There are normal nuclei in the ONL. Near the ELM the Muller cells contain a pair of centrioles and a thin, poorly-developed striated rootlet. There are no dense bodies and myelin figures such as were seen in the Muller cells of the 2K series, but the "satellite-bodies" are present. The MC microvilli are well-developed. In cross-sections no fins were seen on the cones but they are clearly ridged in their surface outlines (Fig. 29).

Fig. 29 demonstrates the general granularity of the material. The degree of granularity varies slightly. The ELM stains very boldly, as do the nuclei and the small 'satellite' bodies seen in close association with the MC centrioles. The microtubules and the ribosomes stain darkly. The cystic spaces of the rod myoid are clear.

The pedicles appear to have a uniformly dense granularity and only rarely show mitochondria. Straight microtubules were seen, but not the tubule-complex seen in the 2K series. The synaptic lamella and all zones of presumed synaptic contact are electron-dense, in both pedicles and spherules. The cone synaptic ribbon was measured and is 0.3 - 0.4 μ long. The rod synaptic ribbon is much longer (0.6 - 1.1 μ), but not as long as those of the 2JS eye.

Area # 9 - An area nasal to the optic disc.

All the other areas examined were in regions temporal to the optic disc.

Light Microscopy

There is a greater incidence of cystic spaces in the rod myoids and a tendency for the cone inner segments to stain more darkly than in the other parts of this eye (Fig. 30). There is some edema in the ONL.

Transmission Electron Microscopy

There were slightly more convoluted ROS present than in the other peripheral areas and very pyknotic cone inner segment and nucleus is seen. Such anomalous individual cells are found randomly, in all areas. There is an increase in the number and the sizes of the rod myoid cystic spaces (compare to Fig. 28).

Area # 4 - The most peripheral area sampled on the temporal side.

This material showed a large number of pathological and/or degenerative changes which are quite unlike the findings in other areas of this retina. While the rest of the retina has a somewhat granular, coagulated appearance, these features are far more severe here. It is very unlikely that what is seen is due to fixation artefact. Disease or trauma are far more likely to be the cause of the aberrations. In many years of fixing normal retinas we have not seen the features detailed below. I do not know anything about the life-history of the monkey and cannot at this stage offer suggestions for the causes of the disintegration seen in this zone.

The following is a list of the observations. There is/are:

(1) Coagulation of the cytoplasm of the photoreceptors with a resulting flocculence and granularity, in varying degrees, and to the extent that some cells are disintegrated (Fig. 31).

(2) A partial or total breakdown of the plasma membranes and other membranes (Fig. 31). Some cone nuclear membranes appear intact while those of neighbouring nuclei cannot be discerned.

(3) Pyknosis and necrosis, in varying degrees from slight to very severe, particularly of the rod outer and inner segments, rod inner and outer fibres, nuclei and spherules (Figs. 31, 32, 33). Some of the spherules are shrunken whether pyknotic or flocculent (Fig. 33).

(4) Swollen, distorted or absent mitochondria but in some cone inner segments mitochondria can be recognised (Fig. 31).

(5) Lysis of some nuclei. The nuclei, especially rod nuclei, are darkly

granular or homogeneously blackened by the stain, and they may be surrounded by pyknotic cytoplasm (Fig. 33).

(6) Contorted outer segment discs which may or may not be pyknotic and which may show pyknotic whorls. Some discs are flocculently disintegrated to the point where they are barely recognisable as outer segment discs (Fig. 32).

(7) Very dark-staining microtubules, cilia (Fig. 31) striated rootlets, cone nucleoli, and also synaptic ribbons and the synaptic-borders of the pedicles (Fig. 33).

(8) Some rod myoids are very enlarged and in cross sections consist of flocculent cytoplasm surrounding a large empty-looking vacuole.

(9) There is edema especially in the ONL.

It is noteworthy that the best preserved membranes are those of the ELM (Fig. 34).

In the light micrograph of a cross-sectional view of the retina (Fig. 35) there can be seen the distribution of the pyknotic rods. The ONL is central in the micrograph. Several pyknotic and distorted nuclei can be seen in the INL. The edema is apparent but the extent of the degenerative changes is apparent only in the electronmicrographs.

The Synaptic Ribbons

Where it was possible to do so, the synaptic ribbons were measured in the photomicrographs. It was found that the synaptic ribbon in the cones measured 0.3 μ - 0.4 μ in the pedicles in both the patched eye (2JD) and the whole eye - argon exposed (2JS). The rod synaptic ribbons were 0.6 - 1.1 μ, with most measuring 0.6 - 0.8 μ in the patched eye; and 0.9 - 1.5 μ in the spherules of the whole eye argon exposed with most of the ribbons measuring 1.4 - 1.5 μ.

Wagner (1973) reported reductions in the number of synaptic ribbons in a dark-reared fish species, and Remé and Young (1977) found the same in the cones of hibernating ground squirrels. Spadaro et al (1978) found that in albino rats synaptic ribbons are largest and most numerous in the light period of the light-dark cycle.

Grün (1980) reported that in adult larval Xenopus and the larvae of the fish, Tilapia, 24 hours of continuous dark resulted in a prevalence of shorter ribbons. There has been the suggestion that an endogenous rhythm accounts for the different ribbon lengths in light and in dark but Grün sacrificed all animals at the same time of the day. Grün says that "the prevalance of shorter ribbons in darkness speaks in favour of a physiological significance of ribbons being long or short. There is perhaps a correlation of ribbon length, the number of synaptic vesicles guided to the junction, and the functional state of the cell".

The measurements made here indicate that the cone synaptic ribbons do not alter in length, but that the rod synaptic ribbon is considerably longer in the retina of the eye exposed to whole-eye argon irradiation than in the patched eye.

DISCUSSION

The gallium arsenide laser irradiated portions of the retina proved very difficult to locate with certainty. In those areas, where, according to the maps, the lesions were located the only specific alteration that could be located in the 1 μ thick sections was a single pigment epithelial cell that failed to take the toluidine-blue stain, seen in one area. In the thin sections, on examination by TEM, some indications of possible laser-induced alterations were seen, but as they were also seen in some parts of the control areas there is no confidence that they are the result of laser-irradiations. Sparse microvilli with fewer melanin granules; loss of microvilli; thicker microvilli; small areas of pigment epithelial hypopigmentation; dense accumulations of large complex melanin-lipofusion bodies; very dense PE cytoplasm; slight scalloping of the PE apical border; accumulations of rough endoplasmic reticulum; accumulations of smooth endoplasmic reticulum; uneven staining of the pigment epithelial cells; "shredded" melanin granules; and alterations in the OS have all been claimed to result from photic insult. These changes are often small and subtle and in assessing 5 eyes, in many different regions, it was possible to see all the above changes in some parts of all the eyes.

In the region of lesion # 10, for example, there was a small area where there was an irregularly shaped PE nucleus, very slight scalloping of the apical PE cell border, areas of light and dark PE cytoplasm side by

side, many ribosomes, profiles of "pinched" SER, and the microvilli seemed to have few melanosomes. Pyknotic COS were present. Should this be considered a laser-affected area? All the features described are seen in many parts of that retina, elsewhere, but here they all happened to be seen all together in one section, and one photomicrograph, and this could be coincidence only. When the micrographs were evaluated without knowledge of the block from which they were obtained, many parts of all the retinas exhibited some areas that showed small deviations from what is considered normal.

In the eyes in this study there were areas of necrosis and there were disturbed COS widespread through a retina. When there are present many anomalies it is extremely difficult to ascribe small changes to the result of laser irradiation. Larger laser lesions, e.g. those created by neodymium laser, are so clear that they cannot be mistaken.

The neodymium laser lesions were very easy to find by thick sectioning and they are described in detail in the results. In other parts of this and other retinas, some slightly irregular-shaped nuclei were seen in the PE but the difference between these and the large, very lobulated nuclei is very large. Slight scalloping of the PE cell apical border is seen in peripheral areas of normal retinas but the scallops seen in the lesion are much larger and correlated with other alterations, e.g. almost total absence of melanin granules in the microvilli, the large number of enlarged and lobulated nuclei, the destruction of the outer segments and some of the inner segments. Fetal-type or "shredded" melanosomes (Feeney et al (1965)) said by Kuwabara (1979) and by Goldman et al (1975)

("striated granules")to result from exposure to photic-insult were seen in control areas of this retina and the other retinas, sometimes more frequently than in the neodymium laser lesions. Bülow (1975) reported that different stages of melanization of the pigment granules were seen in adult normal pigment epithelium. Embryonic melanin granules were not seen in the normal Macaca fascicularis monkey PE. "Pinched" profiles of SER in the PE were seen to be abundant and long; smaller such profiles were seen in all four rhesus monkey eyes, but not in Macaca fascicularis. It is claimed that the mitochondria are easily disrupted by laser irradiation (or trauma generally) but normal, intact, small mitochondria were seen in the PE in the neodymium laser lesion.

The aligned arrays of elongated mitochondria alongside the PE lateral cell border were found in all the 4 rhesus eyes, but not in the area of the neodymium laser and not in the fascicularis monkey. This is a novel finding of unknown significance.

The "lipid globules" of the PE were seen in all the rhesus eyes but not in the fascicularis eye. The large "fetal-like" or "shredded" melanin granules (Kuwabara 1979) were seen in ALL the retinas examined (in their peripheral and foveal parts), and in the neodymium lesion.

These points are discussed to emphasise that the estimation of small changes that result from laser irradiation is fraught with hazards, unless very careful comparisons are made with a number of control areas in the same and other retinas. Attempts were made to quantify, to measure

some of the organellas, for size and incidence, e.g. the complex light-and-dark granules seen in the PE (melanin-lipofuscin). However, this was abandoned as pointlessly time-consuming because:

(1) it is not possible by visual examination of TEM photomicrographs to be sure that the melanin granules have been separated from melanin-lipofuscin bodies;

(2) the variations in the numbers of these dark-staining bodies of the PE is very large even within one small area of a retina;

(3) it is not known how many such complex bodies are "normal" in a "normal" part of the peripheral retina, and which conditions increase or decrease their numbers.

Very small subthreshold lesions are known to be difficult to locate (Adams et al, 1972). Zaret (1965) pointed out that the energy absorbed by different small regions of one retina(because pigmentation varies so much) is so variable that no standardisation is possible, and Lappin and Coogan (1970) demonstrated that different areas of the retina are differently sensitive to laser radiation not only because of pigmentation of the pigment epithelium, but also because of the retinal thickness itself.

That the patched eye resembled the argon exposured eye in most respects may possibly indicate that there is a carry-over effect from the treated to the patched eye. McKechnie and Foulds (1978) unexpectedly found inflammatory cells in the choroid in both eyes of an animal where one was exposed to radiant energy and the other acted as a control.

The striated rootlet of the inner segment was seen frequently in the rods in all the eyes and in the foveal cones and rarely seen in the peripheral cones. Perhaps the dense accumulation of mitochondria may obscure the striated rootlet in the peripheral cones. These cones are larger " fatter" structures and the striated rootlet will more rarely be exposed to view in longitudinal sections than those of the thinner rods and foveal cones.

We regularly saw several approximately parallel, well-developed rootlets within each rod outer segment in both 2J eyes, and in the 2K eyes. The rootlet-organelle is often seen to lie in a longtudinally-oriented vacuole or compartment, which is itself bordered by ribosome-rich cytoplasm. In the literature one striated rootlet is usually reported for each photoreceptor cell inner segment (Sjostrand, 1953; Spira and Millman, 1979; Cohen, 1960; Matsusaka, 1967; Anh, 1969) but Schuscheereba and Zwick (1980) described several rootlets in each rod of the monkey retina. Striated rootlets are reported to be much better developed in rod inner segments than in cone inner segments (Murray et al, 1973; Pedler, 1965). How many striated rootlets there are in any one inner segment is not known and a separate study using cross-sections also would have to be made to establish this. It is also not known whether striated rootlets are permanent or dynamic structures. Schuscheereba et al (1981) found 2.5 x more striated rootlets and centrioles in the apex of the pigment epithelial cells in an eye exposed to whole eye argon illumination, compared to a control occluded eye.

There is a very intimate association of the striated rootlet and

the outer segment. Sjostrand (1959) found the striated filament could be pulled out of the inner segment when the outer segment is separated from it mechanically. What is the function of the striated rootlet? Does it anchor the cilium? Is it the site of transmission of the light-triggered impulse from the outer segment to the synapse? Is it a conductor route for other intercellular stimuli? Is it involved in movement of photo-receptor cells which may alter in length in different lighting conditions (Cohen, 1965; Matsusaka, 1967; Uga et al, 1970; Burnside, 1975) and also in orientation (Enoch, 1972)? Photochemical movements are well-known in lower vertebrates. They may be present but much less marked in higher vertebrates. This has not been carefully investigated. The striated rootlet may be implicated in photomechanical movements and also in movement involved with alighment of the rods and cones (Schuscheereba and Zwick, 1980). The receptors are not parallel to each other across the retina but are aligned with their long axes directed towards the centre of the pupillary aperture, in line with the incoming rays of light (Laties, 1969; Enoch, 1972; Enoch and Hope, 1973). Changes in receptor orientation were found to occur with prolonged darkness (see discussion in Borwein, 1981; Enoch and Birch, in press).

The cone outer segments of the 2K eyes appeared very necrotic, with their discs pyknotic and in various configurations, very rarely in the normal, stacked arrangement. The outer segments of the 2J eyes were normal and showed relatively few convolutions, except in those specific areas where there were degenerating cells. The inner parts of the inner segments of the 2K eyes contained an abundance of autophagic vacuoles, many with

large inclusion bodies, and some of them electron-dense. In the cytoplasm of the Müller cell processes that lay alongside the inner segments there were many electron-dense bodies and inclusions containing whorled membranes. Knob-like protrusions of inner segments cytoplasm into the Müller cell cytoplasm were seen at this level of the cells, suggesting that the undigested residues from the inner segment autophagic vacuoles may be expelled into the Muller cells. In the 2K eyes which contained necrotic outer segments and many autophagic vacuoles, the Müller cells in the region of the ELM and photoreceptor nuclei contained a large number of electron-dense bodies and membranous inclusions. Protrusions of inner segment cytoplasm into MC cytoplasm were seen. The morphologic appearance suggests that the MC may have phagocytic properties. Hori et al (1980), report that in Streptozotocin - diabetic rats Müller cells can digest and eliminate toxic substances and residual bodies in dense bodies resembling lysosomes. In the 2J eyes there were very few such inclusion bodies in the Müller cells.

In the 2K eyes, but not in the 2J eyes, the pedicles often contained very large, swollen mitochondria with twisted cristae. Most of the pedicles of the 2J eyes stained homogeneously. The inner segments of the 2K eyes had normal mitochondria while those of the 2J eyes were often swollen.

It may be that the 2K monkey was an older animal (Müller cell inclusions, necrotic COS, disturbed pedicles) or it had been subjected to some unknown trauma that had affected the cones most.

The cones are generally reported to be more affected by light than are the rods (Ham et al, 1976) independently of wavelength (Lawwill et al, 1977). In this study the cones of the 2K eyes were far more necrotic than those of the whole eye argon irradiated retina, and more affected than tne rods.

Groupings of "complex tubules" were seen regularly in both the pedicles and spherules of the 2K eyes but not in the 2J eyes. The 2J eyes had very coagulated cytoplasm, especially of the inner segments, but the spherules and pedicles were not badly affected. It has been suggested, in a paper by Glees and Spoerri (1977) about tubular structures in the receptor terminals, that these are very labile, and easily destroyed in fixation. Lovas (1971) also reported tubular networks in the photoreceptor terminals of monkey retinas very similar to the ones reported here. The size of the synaptic ribbon of the rod spherule differs in the whole eye exposed retina and the patched retina while the cone ribbon is the same size in both (see page 32).

An interesting finding is that the two centrioles of the inner segment apex are much further apart in the peripheral retina than in the foveas. In published micrographs the centrioles are shown close together.

In small,circumscribed peripheral areas of both the 2J eyes there were pockets containing degenerating photoreceptors, at all levels, and there were even present a few pyknotic cells in the associated INL. However, the number of such areas, and the extent of the degenerative changes seen was much greater in the eye exposed to overall argon irradiation.

Again, we cannot be sure that the greater incidence of pyknosis is due to the argon irradiation. We did not expect to find any area of rod degeneration in the patched eye, and since the cause of this is unknown, it is difficult to attribute the greater area of and the greater degree of pyknosis of the irradiated retina to that treatment. Cones are said to be the more susceptible to light-insult, but here it is the rods that are pyknotic.

It is found throughout this study that the vitreal ends of the ROS are almost always normal in appearance even when other parts show abberations. This was commented on by Adams et al (1972) who found that low levels of coherent radiation with a ruby laser produced alterations in the retina in only one sample, and that consisted of decrease in pigment granules and discharge of these into the subretinal space and barely perceptible swelling and disarray of outer segments of rods and cones as seen by light microscopy. The disarray they saw in the outer segments by TEM we never saw in rod outer segments to the degree they describe; only rarely we saw discs running parallel to the cell axis, at the most distal part of the ROS. Re-arranged rod outer segment discs are seen frequently in the midregions of otherwise normal retinas (Marshall et al 1979) and the COS in this study in the 2K eyes were very altered throughout the retinas. We regularly saw that, throughout the study, OS discs remain intact in the distal section when proximally (especially for cones), and in their midregions (especially for rods) there are alterations in the discs. The fact that the distal outer segment remained intact when the more proximal discs were in disarray is consistent

with the idea that the absorbed light is directly toxic to the outer segments (Adams et al 1972).

Drusen had been seen only in human retinas until Barnett et al (1972) reported them in a baboon. Fine and Kwapien (1978) reported a druse in the retina of an aging rhesus monkey on steroids, and one was seen in this study, so that they obviously do occur in sub-human primates. Barnett et al (1972) found a greater incidence of drusen with age.

Melanin granules form in fetal development and in early post-fetal life and they were thought to be unchanging after that (Hogan et al 1971; Feeney 1978). However, melanin granules that appear shredded, or "embryonic" or juvenile are widely reported in the literature of laser lesions and photic insult (Kuwabara 1979) and in this study they were seen in control areas also. Feeney (1978) suggests that melanin undergoes autophagic remodelling or degradation during the lifetime. She has shown, using enzyme histochemistry and fluorescence microscopy, that there are in the PE two types of melanin-containing complex granules, melano-lipofuscin and melanolysosomes. It was not possible in the present survey to distinguish these. Here they are all called melanin-lipofuscin bodies. The melanolysosomes digest outer segments and produce lipofuscin, the amount of which increases with age.

The laser impact detaches the retina and Anderson et al (1979) in the cat retina saw that after 24 hrs. the PE apical border has a scalloped shape that becomes more pronounced. Johnson and Foulds (1977) in studying retinal detachment in the rabbit saw that the pigment epithelium underwent metaplasia and budded. Protrusions from the

neighbouring cells extended on the apical surface to cut off the budding cell and leave the 'mother' cell in position. Their illustrations are very similar to those in this study. Pigment epithelial cells were also seen to bud off from multinucleate cells in primate retina exposed to argon irradiation (Marshall and Mellerio 1970) and were seen in the subretinal space together with macrophage. They saw an extracellular space between Bruch's membrane and the PE cell. No such space was seen in the neodymium laser lesion studied and it may be that all the free cells in the subretinal space are derived from the PE by budding. Incidentally they also saw an increase in the staining densitites of some components of Müller cells, and that the area of inner and outer segments damaged was smaller than the area of pigment epithelial cell damage. Goldman et al (1975) found that the neodymium laser lesion created damage that was highly localised tc the outer retina, as seen here.

SUMMARY

Eye # 1

The eyes of an untreated Macaca fascicularis monkey were examined. The retinas are well-fixed and normal. Compared to the 4 eyes of M. rhesus treated at LAIR these eyes do not show: "pinched" profiles of smooth endoplasmic reticulum in the pigment epithelium; arrays of elongated mitochondria in the pigment epithelium; cystic spaces in the retina. They do contain "embryonic-like" melanosomes and many phagosomes in the pigment epithelium. The outer segments reach to the apical border of the pigment epithelium.

Eyes # 2, # 3

Control areas

The pigment epithelium contains lipid-like globules, "embryonic-like" melanosomes, "pinched" SER profiles, and arrays of aligned elongated mitochondria at the lateral cell border of the PE cell. The rod outer segments of the periphery and the rods and cones of the fovea reach to the pigment epithelial cell apical border. The rod outer segments usually contain normal discs, and they have convolutions in their mid-zones. The cone outer segments are very disturbed throughout, but less severely in the fovea. In the inner segments of the periphery the 2 centrioles are far apart; in the fovea they are close together. Striated rootlets are seen in many peripheral rods, in the foveal cones, and in a very few peripheral cones. The inner segments contain

many autophagic vacuoles and the Müller cell processes in the ONL contain very many electron dense inclusions and inclusions with membranous and whorled myelin figures.

In the ONL and in the INL there are some pyknotic nuclei and a few dense bodies in the Henle layer and in the outer plexiform layer. On occasional nucleus in the ganglion cell layer is pyknotic.

Gallium arsenide lesions

The gallium arsenide lesions were not seen with assurance. The only specific change seen which is different from anything seen in the controls is a pigment epithelial cell which failed to take the toluidine-blue stain. Others abberations seen which could indicate a laser-induced change were also seen in some control areas. They include:

(1) very small regions of sparse PE cell microvilli with sparse melanin granules;

(2) slight scalloping of the apical PE cell border;

(3) a few rod outer segments in which the discs are re-arranged in longitudinal array at the ROS distal end;

(4) a few pyknotic nuclei in the ONL;

(5) some pyknosis in the Henle fibers; and

(6) Müller cell edema in the ONL.

Neodymium laser lesions

Bruch's membrane contains cells. The pigment epithellum is

affected over a larger area than in the retina. Its apical border is scalloped and bears large protrusions. Free cells, resembling PE cells, lie in the sub-retinal space. Only isolated fragments of IS and OS remain in the lesion center. The ELM is intact even where there are no rods and no cones. The MC microvilli are prominent. The ONL shows considerable pyknosis, necrosis, missing nuclei and edema. The pyknotic nuclei of the INL are displaced laterally from the lesion centre and only the outer ones are pyknotic. The affected part of the Henle layer with dense bodies in it, runs obliquely. There are cystic spaces in the OPL and IPL and edema in the GCL. At the edges of the retina there are only free OS fragments. COS are more affected than rods. The inner segments are club-like and often attach to neighbouring inner segments but contain normal mitochondria. Many synaptic terminals of the photoreceptors are shrunken and electron-dense, or empty.

Within the pigment epithelium, there are areas of dense cytoplasm and areas of hypopigmentation, and dense bodies are seen. The pale nuclei are numerous, large, and much lobulated. Profiles of "pinched" SER are prominent. RER is seen both in the usual apical position and also in the unusual basal position. Normal, small mitochondria are seen in the basal half of the cell. No arrays of aligned elongated mitochondria are present. The hemidesmosomes are pale staining. The change from affected to normal cells is abrupt in the pigment epithelium but not in the retina.

Eyes # 4, # 5

A comparison of the 2JS eye (whole eye exposed to cumulative argon irradiations) and the 2JD eye (patched).

Both eyes contained granular, flocculent, coagulated cytoplasm (particularly of the inner segments) and relatively poorly preserved membranes. In both eyes the cone outer segments are less well preserved than those of the rods, but the pedicles and cone inner segments are better preserved than the rod inner segments and the spherules.

The clearest differences between the two eyes are the following:

(1) In the patched eye (2JD) the outer segments were most often seen to lie appressed to the apical border of the pigment epithelial cell. In the 2JS eye, most often the outer segments were seen to reach only as far as the free edges of the microvillous border, and were often even more distant from the PE cell apical border. In the macula (fovea), all the outer segment tips were distant from the PE cell apical border. In the 2KS eyes the macular rods and cones reach to the PE cell apical borders.

(2) The synaptic ribbons of the pedicles were the same length in both eyes, but those of the spherules were longer in the eye exposed to cumulative argon irradiation.

(3) Pockets of necrotic photoreceptors are seen in both eyes, but the number of such pockets and the intensity and extent of these pyknotic-necrotic degenerative changes is greater in the argon-exposed eye. Since the finding of pockets of necrosis in the patched eye is unexpected there is no certainty that the degenerative changes are the result of argon irradiation. There are also, it seems more scattered

pyknotic nuclei in the ONL and INL in the 2JS eye.

(4) There are far more and far larger cystic spaces seen in the rod myoids of the argon-exposed eye than in the patched eye.

(5) A druse is seen in the PE of the whole eye irradiated retina.

There are listed below a number of observations based on general impressions. They are presented with the caution that there are variations within one retina and they should all be treated as tentative. The observations need confirmation by the examination of several more treated eyes.

In the argon-exposed eye:

(a) The choriocapillaris endothelium is sometimes thickened

(b) Bruch's membrane tends to contain more dense patches and was sometimes seen to be infiltrated by cells.

(c) The pigment epithelium tended to:

(i) have denser darker cytoplasm

(ii) have more ribosomes

(iii) contain more small electron-dense bodies near the basal infoldings

(iv) contain more elongated and large melanin granules within the PE cell body

(v) contain more melanin—lipofuscin bodies

(vi) contain more and larger "shredded" melanin granules

(vii) contain more groupings of the very elongated mitochondria seen at the lateral cell border

(viii) present more nuclei, the outlines of which are uneven

(ix) display more small bulges on the PE apical surface

(d) The inner segment mitochondria tend to be more swollen. (They were not always discernible through the dense coagulated cytoplasm.)

(e) A larger number of deeply-stained striated rootlets are present.

(f) There is more edema in the Müller cells, especially in the ONL and the inner retinal layers.

(g) The centrioles of the inner segment are somewhat further away from each other (0.7 - 1.4 μ) than in the patched eye (1.8 μ). In the macular areas in both eyes, the centrioles were close together.

Compared to the peripheral areas, in the fovea the basal infoldings of the PE cell are larger and the spaces wider; there are relatively few convoluted and disturbed outer segments; the inner segment mitochondria are uniformly swollen and have disorganised or absent cristae. Centrioles of the inner segment are close together; the ELM is very conspicuous because the desmosomal plaques and fibrils stain deeply; and the foveal cone inner segments make apparent contacts with each other.

In eyes treated in a similar way Stuck et al (1980) found very small changes between the treated eyes and the patched eyes and Schuscheereba et al (1981) found that in exposed maculas the OS were distant from the PE and that PE striated rootlets were far more common than they were in the patched eye.

Robbins and Zwick (1979) in Pseudemys, and Zwick and Beatrice (1978) and Zwick et al (1979) in rhesus monkey have found that spectral sensitivity for fine resolution criteria was permanently affected after repeated low-level exposure to diffuse argon laser radiation and the change in spectral sensitivity continued long after cessation of exposure. The only possible distinctive morphological correlate of this finding that emerges from this study is the distance of the foveal COS and rod outer segments from the pigment epithelial cell borders.

A comparison of the 2K and 2J eyes,

The 2K eyes differed from the 2J eyes in the following ways:

1. In the pigment epithelium the cytoplasm contains clusters of smooth endoplasmic reticulum, the centres of which seem pinched together. These profiles are seen in all areas, including the neodymium laser lesion, where they are somewhat longer and more prominent. They are not seen in the 2J eyes.

Clusters of small lipid-like globules occur in the pigment epithelium. They may be lysosomes, or lipofuscin, or lipoidal. They are not seen in the 2J eyes.

2. All the rod outer segments and the foveal cone outer segments reach to the pigment epithelium apical cell border. In the 2JS eye (whole-eye irradiated) the outer segments are distant from the PE cell border.

3. The ROS display many more convolutions than are seen in the 2J eyes.

In the 2K eyes the COS are very disturbed. They have pyknotic discs and the discs are usually in disarray, in various forms.

4. The inner segment mitochondria are reasonably well preserved in the 2K eyes. They are usually either not discernible, or swollen, in the 2J eyes. The autophagic vacuoles are well-developed; they contain a variety of inclusions, many very electron-dense, and so do the MC processes that surround these parts of the inner segments in the outer nuclear layer, in the argon-irradiated eyes.

In the 2J eyes the rod inner segments (myoid regions) frequently have large cystic spaces.

5. The pedicles in the 2K eyes are often pyknotic, or often contain very swollen mitochondria with disorganized or absent cristae. In the 2J retinas, where there are necrotic areas, it is the spherules that are severely affected.

In the 2K eyes, the receptor synaptic terminals often display a tubule-complex.

6. There are more cystic spaces in the innermost retinal layers of the 2K eyes than are present in the 2J eyes.

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FIGURE LEGENDS

Fig. 1. M. fascicularis. Normal retina. Pigment epithelium and outer segments. Note the basal infoldings, densities in Bruch's membrane, long melanin granules in the microvilli and round melanin granules in the cell body.
x 3,800

Fig. 2. M. fascicularis. Normal retina. The inner limiting membrane is wide. Vitreal condensations can be seen on the ILM. The axons of the nerve fibre layer are filled with neurotubules. Dark MC processes can be seen between the axons.
x 15,000

Fig. 3. M. rhesus: Pigment epithelium of 2KS eye (Block 2KS6). A large "embryonic-like" or "shredded" melanosome, many melanin-lipofuscin bodies are present, and also profiles of pinched SER (arrows). Small mitochondria and ribosomes can be seen near the basal infolds which are not very conspicuous. At Bruch's membrane hemidesmosomes stain clearly.
x 6,000

Fig. 4. 2KS eye. Rod outer segment discs are more-or-less normal but show convolutions. The cone outer segments have pyknotic-necrotic discs grouped in unusual configurations.
x 5,000

Fig. 5. 2KS eye. The normal discs in the convoluted mid-region of the rod outer segment are displayed.
x 15,000

Fig. 6. 2KS eye. Rod outer segments displaying striated rootlets and mitochondria.
x 15,000

Fig. 7. 2KS eye. Henle fibres, one of which is pyknotic (arrow) and pyknotic pedicles, one of which contains very swollen mitochondria, can be seen.
x 3,800

Fig. 8. 2KS eye. Spherules and pedicles can be seen. One pedicle has mitochondria and a "tubule-complex" (arrow). The second pedicle is missing. A "tubule-complex" can also be seen in one of the spherules.

x 6,000

Fig. 9. 2KS eye. The synaptic vesicles can be seen. 2 groupings of the "tubule-complex" are illustrated.

x 24,000

Fig. 10. 2KS eye. Inner nuclear layer. Around some of the darker-staining inner nuclei can be seen parallel-arrays of RER (arrows).

x 2,400

Fig. 11. 2KS eye. Foveolar area. Light micrograph. The long thin cone outer segments display nodules and convolutions. The nuclei of the foveolar cones are distant from the ELM. Some cones can be seen reaching to the PE.

x 1,200

Fig. 12. 2KS eye. Pigment epithelium and outer segments of the foveola. The cone outer segments display convolutions and uneven borders. A large "shredded" melanin granule is present. The basal infoldings form a light border to the cell. A cone phagosome can be seen in a microvillus.

x 3,800

Fig. 13. 2KS eye. Pigment epithelium. "Embryonic-like" melanin granules, pinched SER profiles, (arrows) lipid-like globules are present.

x 9,500

Fig. 14. 2KS eye. Foveolar CIS shows two centrioles close together, and a striated rootlet. The apex of the inner segment is devoid of mitochondria.

x 20,000

Fig. 15. 2KS eye. Foveola. The ELM is well-developed (see Fig. 15a). The desmosomes have many dark-staining fibrils. The Müller cells contain satellite bodies (arrow) associated with the centrioles of this area of the MC, and electron-dense inclusion bodies and other inclusions. The inner segments contain autophagic vacuoles.

x 6,000

Fig. 15a. 2KS eye. A knob-like protrusion from the inner segment, near the autophagic vacuoles, projects into the MC cytoplasm. The Müller cell, vitreal to the ELM, contains a centriole, the satellite bodies, some microtubules, and an inclusion body with whorled and electron-dense contents.

x 24,000

Fig. 16. 2KS. Area of lesion # 8. Pigment epithelium and outer segments. The outer segments do not reach the PE. Note that there is a pyknotic COS present, one of the ROS has the discs re-arranged so that they are largely longitudinal in orientation. "Pinched" profiles of SER are present (arrow).

x 3,800

Fig. 16a. 2KS. Area of lesion in block 2KS4. Light micrograph of a thick section. Note that the outer segments are distant from the PE. One PE cell is very light, having failed to take the toluidine-blue stain.

x 3,000

Fig. 17. 2KD. Rod and cone outer segments showing (a) rod outer segments with discs in normal array, and one with a nodular convolution; (b) a disturbed COS - showing also its cytoplasmic component.

x 6,000

Fig. 18. 2KD eye with neodymium laser lesion. A light micrograph shows the overall shape of the laser lesion. Free cells can be seen lying in the subretinal space near the PE. Outer segments and inner segments are absent from the lesion centre. There are pyknotic nuclei in the ONL, and a light band in the Henle fiber layer is oriented obliquely towards a few pyknotic nuclei in the outer part of the INL.

x 400

Fig. 19. 2KD eye. Neodymium laser lesion. Light micrograph. Outer and inner segments are absent. The ONL contains pyknotic nuclei; some nuclei are missing, and there is edema. The Henle fiber layer has a light band obliquely directed. A few pyknotic nuclei can be seen in the outer row of the INL.

x 1,200

Fig. 20. 2KD eye. Neodymium laser lesion. The pigment epithelium has a very scalloped margin. Melanin granules are absent from the microvilli. Lobulated nuclei are present. Free cells lie close to the PE border.

x 1,500

Fig. 21. 2KD eye. Neodymium laser lesion. Normal mitochondria are present in the basal part of the PE cell near the shallow basal infoldings.Lipid-like globules are present. Elaborately interdigitated lateral cell borders are present (arrow).

x 9,500

Fig. 22. 2KD eye. Neodymium laser lesion. Club-like inner segments can be seen and fragments of cells. A macrophage-like cell, containing outer segment discs is present. The MC microvilli can be seen, and the ELM.

x 3,800

Fig. 23. 2KD eye. Neodymium laser lesion. There are inner segment fragments, and club-like stumps can be seen attaching to each other. The ELM is present. The ONL displays various degrees of necrosis and edema, and some nuclei are missing.

x 1,500

Fig. 24. 2KD eye. Neodymium laser lesion. The innermost part of the ONL shows 3 very necrotic nuclei, and pyknotic and necrotic structures can be seen in the Henle fiber layer.

x 6,000

Fig. 25. 2KD eye. Neodymium laser lesion. Pyknotic and necrotic receptor synaptic terminals are seen, and pyknotic bodies in the fiber layer.

x 3,800

Fig. 26. 2JD - patched eye. The polarity of the PE cell is well displayed. A group of aligned, very elongated mitochondria is present (arrow). The discs of the ROS are in the normal stacked array and the ROS abut on the apical border of the PE cell.

x 3,800

Fig. 27. 2JD - patched eye. The granular appearance of the tissue can be seen. Many striated rootlet strands can be seen in the inner segment. The COS shows vesicular profiles and unevenly stained discs.

x 9,500

Fig. 28. 2JD - patched eye. Cystic spaces in the inner segments of the rods can be seen.

x 1,500

Fig. 29. 2JD - patched eye. Cross-sectional view of the photoreceptor inner segments and the ELM. MUller cell microvilli can be seen around the RIS and CIS. The cystic spaces are within the rods.

x 2,400

Fig. 30. 2JD - patched eye. Light micrograph. Area # 9. There are many cystic spaces in the RIS (see Fig. 28). The CIS are dark-staining.

x 1,200

Fig. 31. 2JD - patched eye. Area # 4. A region of the eye shows necrosis, most particularly of the rods. Here the pyknotic RIS are displayed. Some cells are disintegrated (upper righthand corner).

x 6,000

Fig. 32. 2JD - patched eye. Area # 4. In an area of necrosis the outer segments show strange configurations and pyknosis. Plasma membranes are not preserved.

x 6,000

Fig. 33. 2JD - patched eye. Area # 4. Spherules are necrotic and shrunken; some are flocculent. Necrotic rod nuclei lie on the lefthand side.

x 2,400

Fig. 34. 2JD - patched eye. Area # 4. The best preserved membranes are those of the ELM in an area where the membranes are very poorly preserved. The generally coagulated appearance of the cytoplasm is clearly displayed. Some pyknotic rods are present.

x 3,800

Fig. 35. 2JD - patched eye. Area # 4. Light micrograph, cross-sectional view of the retina displaying the distribution of the pyknotic rods from their inner segments at the base of the photograph to their synaptic terminals. A few pyknotic nuclei can be seen in the INL.

x 1,200

Fig. 36. 2JS. Argon irradiated. The pigment epithelium displays a large array of aligned elongated mitochondria and concentrically arranged long mitochondria (arrows). The basal infoldings are not prominent. Many small electron-dense bodies are present near the basal infoldings. Large "striated" melanin granules are present.

x 8,000

Fig. 37. 2JS. Argon irradiated. A single large druse is present (arrow) in the base of the pigment epithelial cell. Many ribosomes can be seen.

x 15,000

Fig. 38. 2JS eye. Argon irradiated. The outer segments are distant from the apical border of the PE cell. There are elongated mitochondria present (arrow) and an accumulation of melanin and melanin-lipofuscin bodies.

x 3,800

Fig. 39. 2JS eye. Argon irradiated. Pyknotic material is seen around the ROS. For the most part the discs are in the normal stacked array.

x 8,000

Fig. 40. 2JS eye. Argon irradiated. COS show some vesiculation and uneven staining of the discs.

x 8,000

Fig. 41. 2JS eye. Argon irradiated. RIS contain large cystic spaces. In the lefthand one a striated rootlet can be seen traversing the cystic space supported by cytoplasmic strands. Mitochondria can be seen in the CIS.

x 8,000

Fig. 42. 2JS eye. Argon irradiated. Area showing necrosis. There are pyknotic nuclei in the ONL; pyknotic RIS and rod inner fibers. Lysis and disintegration of nuclei can also be seen.

x 1,500

Fig. 43. 2JS eye. Argon irradiated. Degenerative changes can be seen in this thick section. The ONL contains many pyknotic cells. Fewer pyknotic cells are present in the INL. Pyknosis can be seen in the RIS and inner fibers and spherules Large cystic spaces are present in the RIS.

x 1,200

Fig. 44. 2JS eye. Argon irradiated. Area of necrosis. The micrograph displays cystic spaces in rod inner segments, pyknotic and necrotic rod inner segments, rod nuclear pyknosis, and edema in the ONL.

x 2,000

Fig. 45. 2JS. Argon irradiated eye. Area of necrosis. The degenerating ONL is clearly displayed. Nuclei are missing. There is considerable edema.

x 1,500

Fig. 46. 2JS. Argon irradiated eye. The ganglion cells contain swollen mitochondria. There are cystic spaces in the GCL. The ILM is intact.

x 3,200

Fig. 47. 2JS. Argon irradiated eye. Macula. Light micrograph of the fovea. There are many melanin pigment granules in the microvilli of the PE. There are swollen mitochondria in the inner segments.

x 1,200

Fig. 48. and Fig. 49. 2JS. Argon irradiated eye. Macula. Many arrays of aligned elongated mitochondria are present (arrows). The cytoplasm is dense. The outer segments do not reach to the PE cell apical border. Many small mitochondria are present.

x 2,400

Fig. 50. 2JS. Argon irradiated eye. The pigment epithelial cell displays lipid-like globules and a pyknotic nucleus.

x 12,600

Fig. 51. 2JS. Argon irradiated eye. Fovea. Swollen mitochondria are seen in inner segments. A cone outer segment shows uneven staining of the discs (arrow). The cone discs are generally in orderly array, but convolutions are seen in the mid-regions of the COS.

x 3,200

Fig. 52. 2JS. Argon irradiated eye. Fovea. A cone outer segment shows a calycal process, discs separated from each other in groups, and a dense staining elongated structure lies alongside the discs in the ciliary backbone.

x 20,000

Fig. 53. 2JS. Argon irradiated eye. Foyea. Swollen mitochondria in the ellipsoid of the cone. 2 centrioles and a striated rootlet can be seen, and 2 calycal processes.

x 12,600

Fig. 54. 2JS. Argon irradiated eye. The elongated CIS of the foveolar contain swollen mitochondria. The CIS are wider near the ELM and taper towards their distal ends. Many contain striated rootlets. They contact each other by small protruberances.

x 3,200

Fig. 55. 2JS. Argon irradiated eye. Foveola. Cone inner segments contain cystic spaces. The ELM is well preserved. In the MC there are satellite bodies and other small inclusion bodies.

x 10,000

Fig. 56. 2JS. Argon irradiated eye. Foveola. The cluster of satellite bodies in the MC cytoplasm, close to the ELM, is clearly displayed here.

x 20,000

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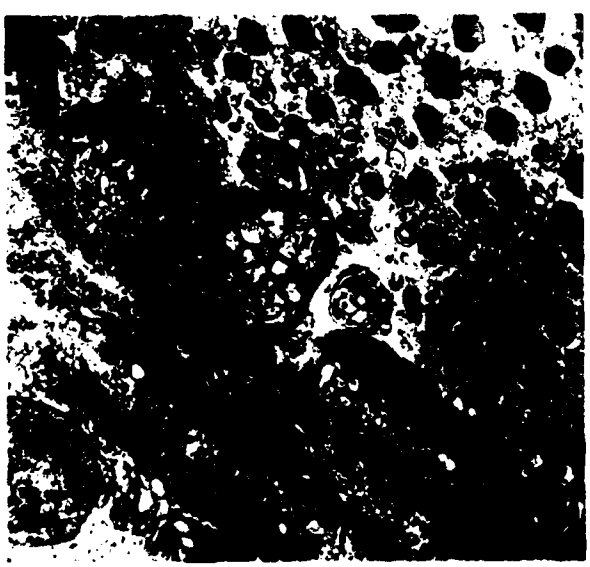

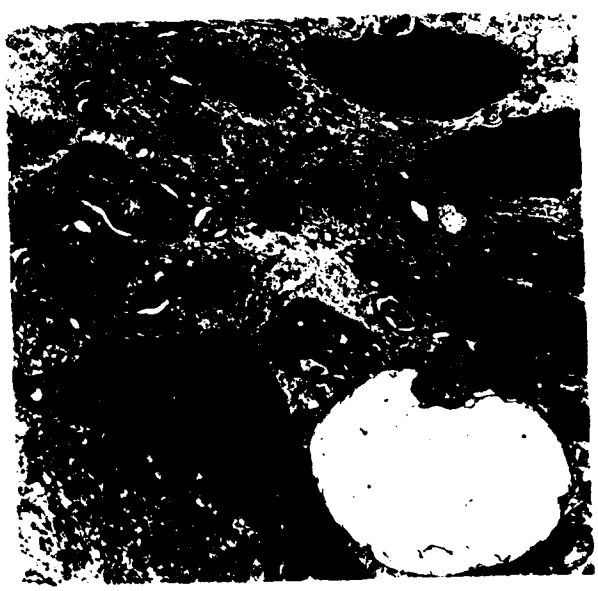

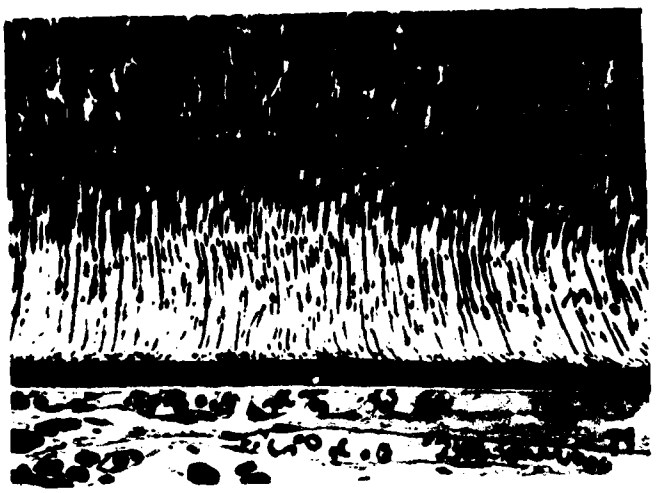


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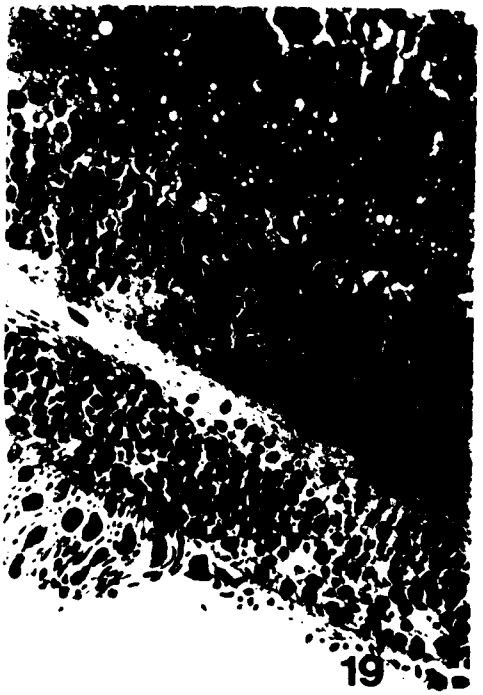

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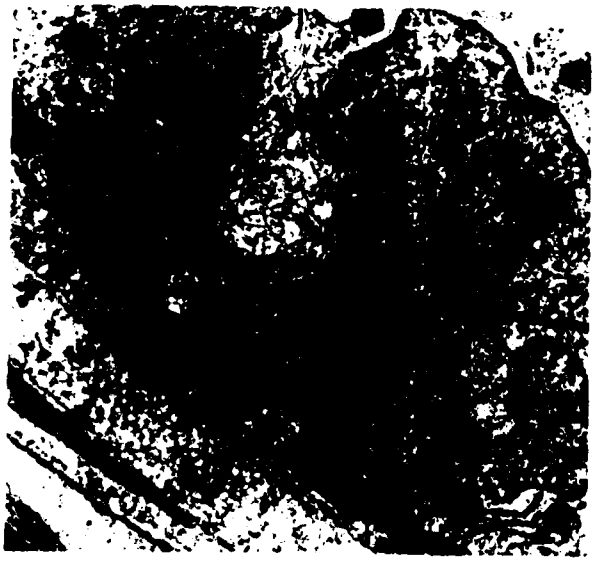

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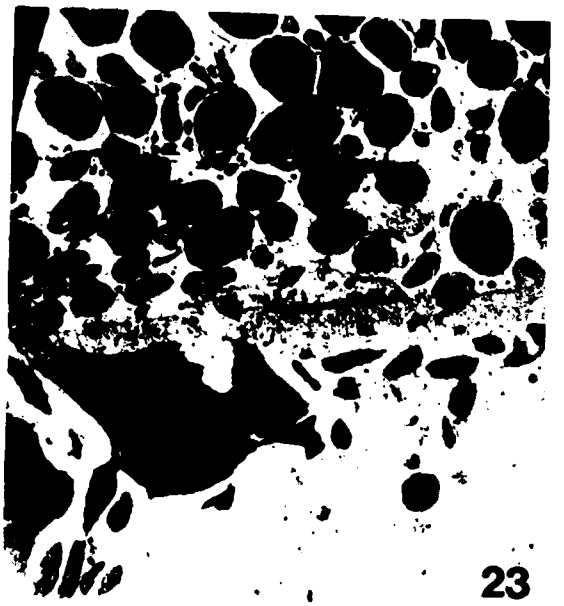

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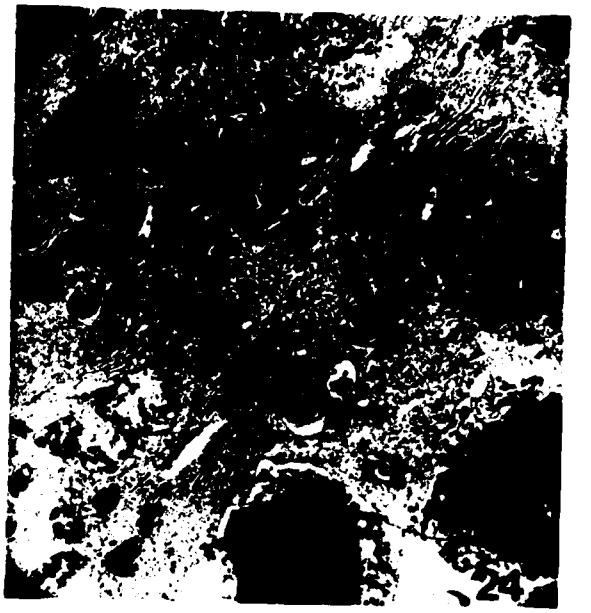

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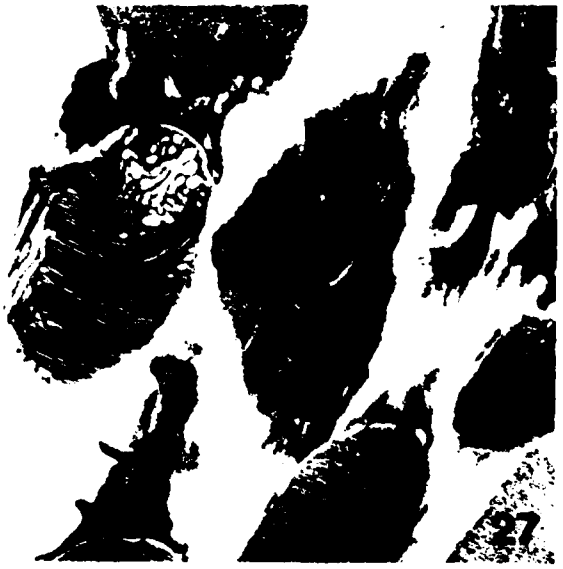

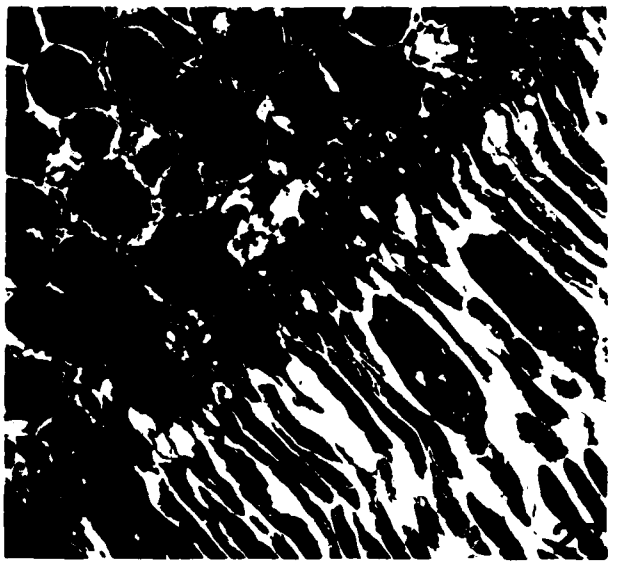

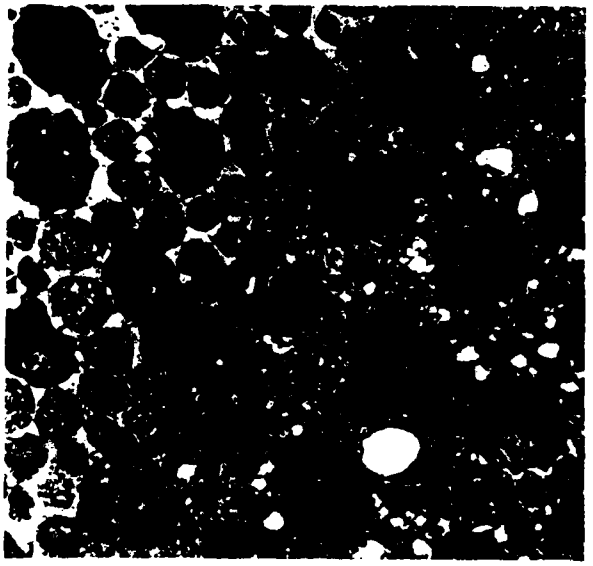

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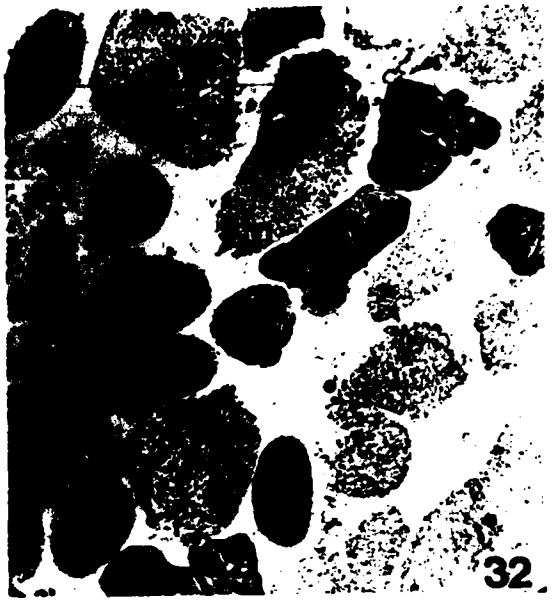
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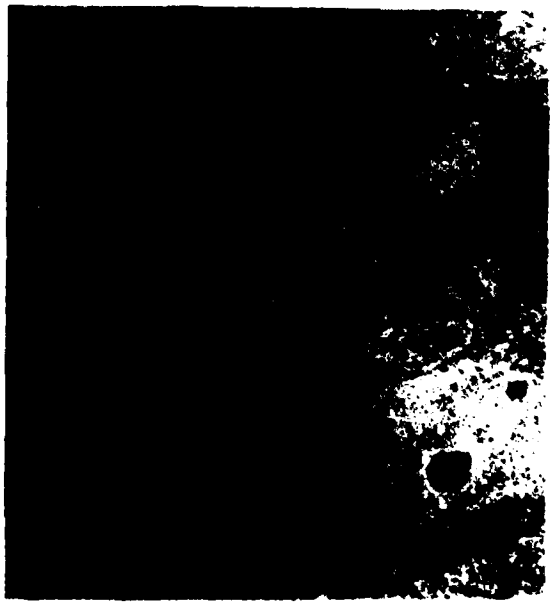

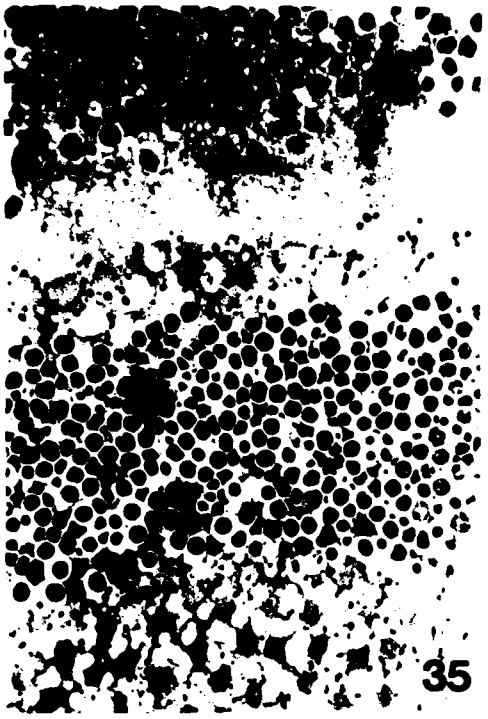

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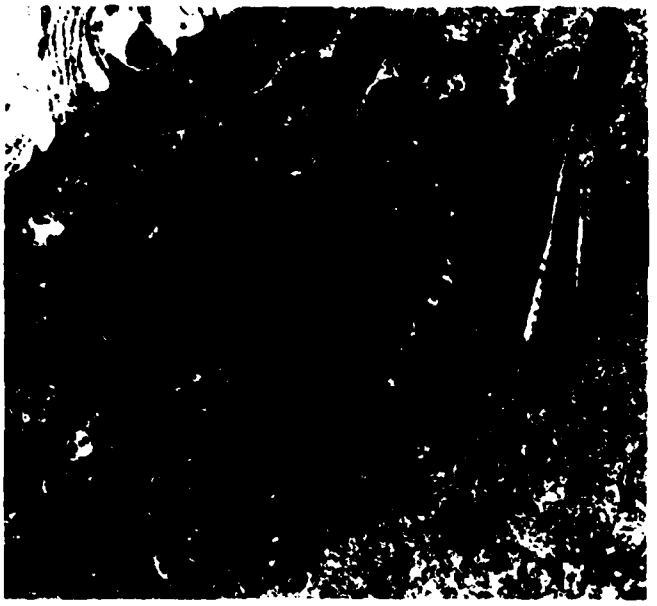

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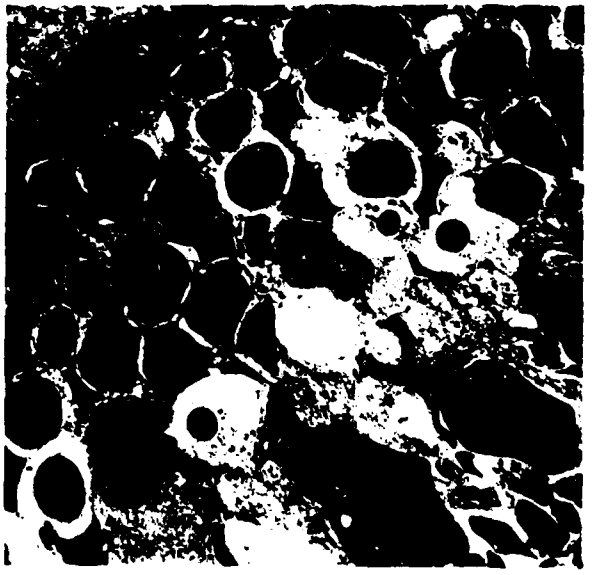

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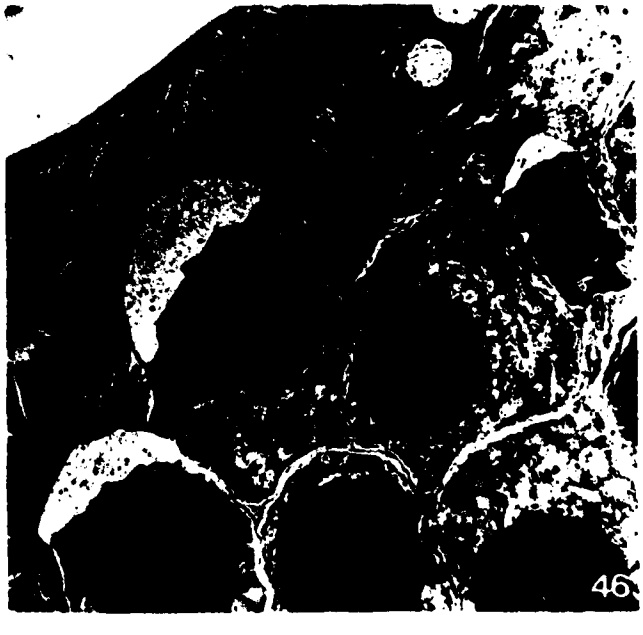

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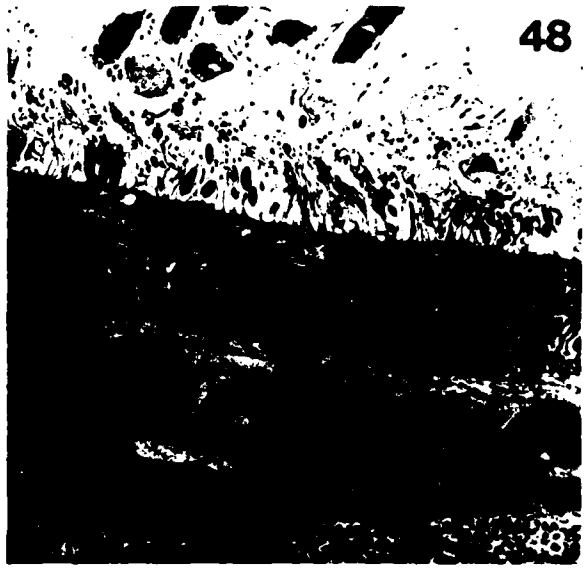
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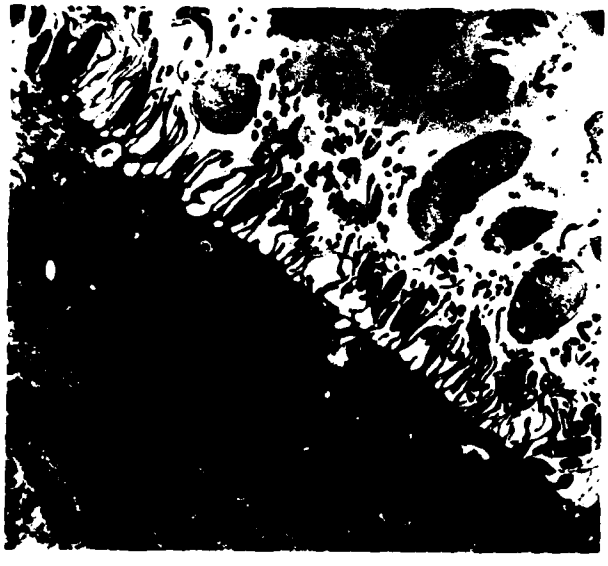


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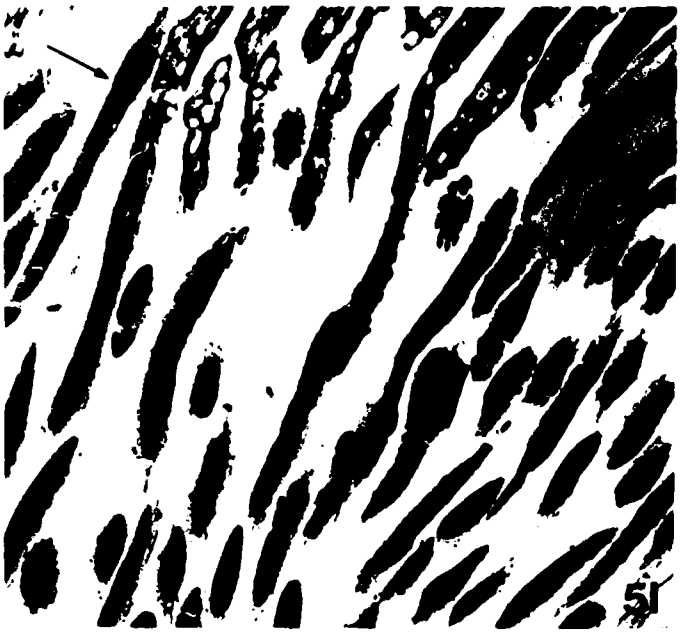

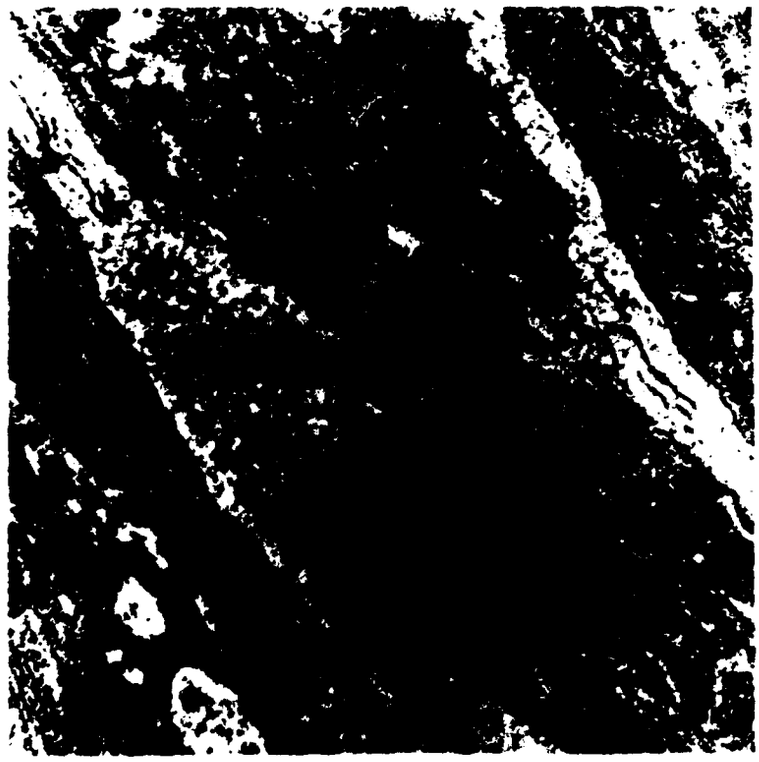

APPENDIX I

Abbreviations used

CIS	cone inner segment/s
COS	cone outer segment/s
ELM	external limiting membrane
GCL	ganglion cell layer
ILM	inner limiting membrane
INL	inner nuclear layer
IPL	inner plexiform layer
MC	Muller cell/s
MLM	middle limiting membrane
MV	microvillus/microvilli
NFL	nerve fiber layer
ONL	outer nuclear layer
OPL	outer plexiform layer
PE	pigment epithelium
RER	rough endoplasmic reticulum
RIS	rod inner segment/s
ROS	rod outer segment/s
SER	smooth endoplasmic reticulum
TEM	transmission electron microscopy

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* Supported by USAMRDC.

ø These publications result from this granting period.

END